Published in final edited form as:
Curr Opin Rheumatol. 2013 November ; 25(6): . doi:10.1097/01.bor.0000434668.32150.e5.

Measuring Response in the Gastrointestinal Tract in systemic sclerosis

Dinesh Khanna[1], **Vivek Nagaraja**[1], **Heather Gladue**[1], **William Chey**[1], **Mark Pimentel**[2], and **Tracy Frech**[3]

[1]University of Michigan, Ann Arbor, MI

[2]Cedars Sinai Medical Center, Los Angeles, CA

[3]University of Utah, Salt Lake City, UT

Abstract

Purpose of review—Gastrointestinal tract (GIT) involvement in systemic sclerosis (scleroderma, SSc) is the most common internal complication. This review discusses the outcome measures to measure GIT involvement in clinical care and trials.

Recent findings—Patient-reported outcome measures have been validated (UCLA SCTC GIT 2.0 and NIH PROMIS® scales) in SSc-GIT. Multiple objective measures are available to assess mucosal involvement and motility in GIT. However, these need to validated in SSc for trials.

Summary—GIT is a common cause of morbidity and has negative impact on quality of life in SSc. Recommendations are given for trial design and evaluation of GI involvement in SSc.

key words/phrases

systemic sclerosis; gastrointestinal involvement; UCLA SCTC GIT 2.0; outcome measures

Introduction

Gastrointestinal tract (GIT) involvement in systemic sclerosis (scleroderma, SSc) is the most common internal complication of this autoimmune disease characterized by progressive multi-organ vasculopathy and fibrosis (1). While the pathogenesis of SSc is not well understood, it has been proposed that akin to the cutaneous manifestations of this disease an early vascular lesion (vasculopathy) results in altered intestinal permeability, which is followed by neural dysfunction, fibrosis and loss of function (2). While circulating autoantibodies to myenteric neurons are reported in SSc (3, 4), it is unclear whether these autoantibodies are responsible for or a result of GIT dysfunction. Regardless of its etiology, progressive GIT vasculopathy and fibrosis results bothersome symptoms including esophageal reflux, bloating, distention, constipation, diarrhea, and fecal soilage. The symptoms of GIT dysfunction are challenging for the physician to assess since it may be the result of organ damage or secondary effects of therapeutics used for other disease manifestations, or poor motility, such as small intestine bacterial overgrowth. As such, understanding the etiology of GIT symptoms and measuring response of therapeutics requires a combination of patient reported outcomes and imaging modalities. This review

Correspondence to: Dinesh Khanna, MD, MSc, Director, University of Michigan Scleroderma Program Division of Rheumatology/ Dept. of Internal Medicine Suite 7C27, 300 North Ingalls Street, SPC 5422, Ann Arbor, MI 48109, khannad@med.umich.edu, Phone: 734.647.8173, Fax: 734.763.5761.

discusses tools for measuring response in the GIT in SSc in clinical care and in clinical trials.

There are various tools available to assess the presence and severity of GI involvement in SSc (Table 1). In general, presence of GI-specific symptoms and abnormal finding on an objective test makes a diagnosis of GI involvement. However, there are little data available in SSc that longitudinally assesses response to therapy in SSc-associated GIT involvement.

Patient Reported Outcome Measures

There are validated patient reported outcome (PROs) measures for GIT involvement. This section will discuss PROs studied in patients with SSc. Later sections (recommendations) will also discuss other PROs.

UCLA SCTC GIT 2.0 The UCLA Scleroderma Clinical Trial Consortium GIT 2.0 [UCLA SCTC 2.0](5, 6) includes 34 items and 7 multi-item scales (reflux, distention/bloating, diarrhea, fecal soilage, constipation, emotional well-being, and social functioning) and a total GIT score to assess HRQOL and GIT symptoms severity in SSc. All scales are scored from 0.00 (better HRQOL) to 3.00 (worse HRQOL) except the diarrhea and constipation (range from 0.00–2.00 and 0.00–2.50, respectively). The UCLA GIT 2.0 provides a total score of GIT severity and calculated by summation of all scales (except constipation) and ranges from 0.00–2.83. The GIT 2.0 takes 6–8 minutes to complete and was found to have acceptable feasibility, reliability (test-retest and internal consistency) and validity in different observational studies.(5, 7–14)

The severity for scales was calculated using 3 anchors (“In the past 1 week, how severe were your gastrointestinal (gut, GI) symptoms) overall/upper/lower symptoms?” with responses ranging from “No gut symptoms” to “Very severe” symptoms. These were assessed using original published data and data collected in a National Scleroderma Foundation online survey (Table 2). The patients have been classified as “None-to-Mild” symptoms, “Moderate” symptoms, and “Severe-to-Very Severe” symptoms.

UCLA GIT 2.0 has been assessed in longitudinal studies and minimally important differences have been published(5). In an open-label study, 10 consecutive patients with SSc and a moderate-to- severe distention/bloating score but otherwise stable organ disease not requiring any medication adjustment such as change in calcium channel blocker dose, immunosuppression, initiation of a prokinetic or antibiotic, or any other clinical intervention. Subjects completed the UCLA SCTC GIT 2.0 assessment at baseline. Subjects were treated with daily probiotics and significant improvements were noted in the total score and the scale of reflux, bloating/distention, and emotional well-being scales after two months of daily probiotic use(15).

Malnutrition Universal Screening Tool

Malnutrition is common in SSc and may be associated with progressive GIT involvement (16, 17). All SSc patients should be screened for malnutrition, but this may prove challenging as malnutrition may be multifactorial in origin and not reflective in simple markers such as serum albumin (18, 19). The Malnutrition Universal Screening Tool (MUST) is a five-step screening tool designed to identify patients at risk of malnutrition across the whole range of health care settings has successfully detected malnutrition in SSc (20–22). However, while this tool is helpful for identifying its severity and facilitating a multidisciplinary approach for the management of malnutrition, it does not adequately assess the symptomatology contributing to its occurrence.

Subjective Global Assessment (SGA) is an assessment tool that uses aspects of the history (including, weight change, dietary intake, gastrointestinal symptoms, functionality) and physical exam (including wasting, edema, and ascites) to classify nutritional status (20, 23). In one small study of SSc, the soilage, social function and emotional subscores on the GIT 2.0 were associated with SGA nutritional status (20). It is feasible in the clinical setting, supplement the UCLA SCTC GIT 2.0 for assessing nutritional status, and captures aspects of loss of subcutaneous tissue, muscle wasting, and weight loss. However, it does not correlate with disease duration and may not be the best single tool for measuring the response of the GIT in SSc (20).

The National Institutes of Health Patient-Reported Outcomes Measurement Information System (PROMIS®) roadmap initiative is a cooperative research program designed to develop, evaluate, and standardize item banks to measure PROs across different medical conditions as well as the US population (www.nihpromis.org)(24). It has comprehensive items banks that assess physical, mental, and social well-being. The GIT Symptoms Item Bank assesses eight domains of GI symptoms: (1) GI Pain; (2) Bloat/Gas; (3) Diarrhea; (4) Constipation; (5) Bowel Incontinence/Soilage; (6) Gastroesophageal Reflux; (7) Nausea/Vomiting; and (8) Disrupted Swallowing. The scale has been tested in patients with SSc and GIT involvement in a longitudinal study and will be published in near future.

Imaging modalities

This section discusses the imaging modalities used to assess mucosal involvement and motility in patients with GIT disorders.

Esophageal and Stomach

The choice of an imaging modality in assessment of SSc GIT disease may be assisted by use of a patient reported outcome, which quantifies severity of symptoms or response to therapeutics. However, esophageal manifestations of SSc may not always be symptomatic (25). Nonetheless, early diagnosis of esophageal involvement remains important as a delay may increase the risk of complications, such as Barrett's or interstitial lung disease (2, 26). Diagnostic tools used to identify esophageal pathology in SSc may include modified barium swallow study (MBSS), manometry, impedance, endoscopy, and endoscopic ultrasound (EUS). Once identified, response to therapeutics may be identified on repeat imaging.

A MBSS can clarify abnormalities of both oropharyngeal and esophageal swallow function. As such the functional interrelationship between abnormalities of oropharyngeal and esophageal swallowing as well as impaired clearance of the esophagus can be identified with this test (27). MBSS is usually the first test ordered for evaluation of dysphagia. While it does not characterize refluxate and is not sufficiently sensitive to determine response to reflux treatment, it is helpful for identification of aspiration and stricture (28).

Reflux may occur due to abnormalities in the relaxation of the lower esophageal sphincter (LES), inhibition of the diaphragmatic crural sling, or change in the positive pressure gradient present between the stomach and the gastroesophageal junction (29).

Esophageal manometry allows the study of esophageal motility by measuring pressure profiles in the esophagus. The recent development of high-resolution esophageal manometry has further enhanced the ability to study motility in much greater detail by providing pressure measurements at more levels along the esophagus (30). The most significant limitation of pH-metry is its poor capacity to detect episodes of alkaline reflux, it cannot determine the characteristics of the refluxate, the height reached by the refluxate in the

esophagus, or the mechanism of its clearance (31). Nonetheless, the use of manometry in addition to 24-hour combined pH-impedance monitoring may reveal esophageal motility disorders that can predispose to chronic respiratory symptoms and allow detection of reflux regardless of pH (32, 33).

Endoscopy can be used to evaluate the condition of the esophagus in SSc and to evaluate for erosive lesions, gastric antral vascular ectasia (GAVE; "watermelon stomach") and can monitor the clinical course of Barrett's esophagus. EUS can accurately demonstrate the layers of the esophageal wall (34). Capsule endoscopy may also be used to evaluate the esophagus, small bowel, and colon (35), with possible identification of occult gastrointestinal bleeding from GAVE possibly its most important indication in SSc.

Computed tomography and magnetic resonance imaging may have features of SSc, such as dilation of the esophagus, but are not diagnostic (36). Lastly, (18)F]fluorodeoxyglucose (FDG)-positron emission tomography (PET) provides robust and reproducible data for early metabolic response assessment in various malignancies (37), it has not yet been used for assessment of GIT disease in SSc.

Small Bowel

The entire small bowel can be visualized in a noninvasive manner by CE, but both visualization and therapeutic management can be performed with deep enteroscopy (ileocolonoscopy) techniques, including balloon-assisted and spiral enteroscopy (38). CT enterography is another modality for the evaluation of small bowel disease, which has the potential additional advantages of detecting extraluminal complications, but is not the standard of care in SSc (39).

Large Bowel and Rectum

Endoscopy directly visualizes the large bowel and rectum, but it does not provide diagnostic motility information. Plain radiograph, rectal barium study, and CT may be used to rule out large bowel obstruction (LBO) as a complication of SSc (40). Defecography is helpful to evaluate the anorectal area. In this procedure, a radiopaque substance which is the consistency of normal stools, is introduced into the rectum and the patient is then seated on a specially designed seat which measures movements induced by evacuation of the rectum(41). In the setting of SSc this procedure can be used to evaluate rectal outlet obstruction (obstructed defecation) symptoms, suspected conditions such as internal rectal intussusception, pelvic floor dysynergia, rectocele or sigmoidocele. Another possible complication of SSc, pneumatosis intestinalis is characterized by the appearance of intramural clusters of gas in the small and large bowel wall on X-ray or computed tomography and often is accompanied by free air in the peritoneal cavity (42).

Recommendations for validating outcome measures in SSc-GIT involvement

—These recommendations are based on the Scleroderma Clinical Trial Consortium GI Working Group meeting at the last Annual American College of Rheumatology meeting held in November 2012 at Washington D.C. There are separate ongoing efforts to develop recommendations for clinical trials in SSc and will be published elsewhere. For the each of the symptoms below, the data should be evaluated for feasibility, reliability (including test-retest and internal consistency), and validity (including sensitivity to change).(11, 12) A feasible measure is accessible, easily interpretable, and associated with low cost. Reliability (precision) is extent to which a measure yields the same score each time it is administered if underlying health condition has not changed. A reliability coefficient of 0.90 or higher (means that 90% of the score is accurate while the remaining 10% denotes error) is considered satisfactory for individual comparisons and 0.70 or higher is considered

satisfactory for group comparisons. Validity is the extent to which the score a health measure yields accurately reflects the health concept and includes face (sensible), content (comprehensive), construct (measures or correlates with a theorized health construct), and criterion validity (predicts or correlates with 'gold standard'). Sensitivity to change, an aspect of construct validity, assesses if an instrument score changes in the right direction when underlying health construct changes; the ability of an instrument to detect clinically important change is crucial to their usefulness as an outcome measure in a clinical trial.

The outcome measures are chosen based on review of GIT literature and expert opinion. The group agreed on further evaluating outcome measures in patients with signs and symptoms of gastroesophageal reflux disease, gastroparesis, small bowel bacterial overgrowth, constipation, and rectal incontinence.

Gastroesophageal Reflux Disease (GERD)—Although heartburn is the most common symptom of GERD, other symptoms may include odonophagia, mouth ulcers, substernal chest pain, chronic laryngitis, chronic nocturnal cough, and asthma(43).

Proposed inclusion criteria for GERD involvement

1. Symptoms of GERD present for at least 3 of last 7 days
2. Abnormal 24 pH probe, pH impedance study, barium swallow (showing spontaneous reflux) or upper gastrointestinal endoscopy
3. Plan to initiate GERD-specific therapy (H2 blockers/proton pump inhibitor) to assess sensitivity to change over time

Outcome measures administered at baseline and 4 weeks: Reflux Disease Questionnaire(44), UCLA SCTC GIT 2.0(5), Quality of Life in Reflux and Dyspepsia (QOLRAD)(45).

The Reflux Disease questionnaire consists of six symptom items that has a 4-point scale (0–3) for both frequency and intensity, 0 =absent symptoms and 3 =present daily or severe symptoms(44). QOLRAD is a validated scale using 25 items with 5 dimensions (physical/social functioning, emotional distress, sleep disturbance, diet problems and vitality). Responses are based upon a 7- point Likert scale that is used to assess the amount of patients' distress, with 1 being the most distress. The total score is calculated as a mean of each dimension (45). The QOLRAD and Reflux Disease Questionnaire have been assessed for reliability and validity in multiple clinical trials(46–50).

Gastroparesis—Patients with SSc develop clinical symptoms of gastroparesis, including bloating, nausea and vomiting, abdominal pain, and excessive flatulence; these symptoms may contribute to significant weight loss.

Proposed inclusion criteria for gastroparesis

1. Symptoms of distention/bloating AND/OR nausea/vomiting present for at least 3 of last 7 days
2. Abnormal solid phase gastric emptying study
3. Plan to initiate promotility agents to assess sensitivity to change

Outcome measures administered at baseline and 4 weeks: Gastroparesis Cardinal Symptom Index(51), UCLA SCTC GIT 2.0(5)

The Gastroparesis Cardinal Symptom Index is based on post-prandial fullness/early satiety (4 items), nausea/vomiting (3 items), and bloating (2 items). All three subscales are given a score from 0 to 5 with the higher scores reflecting greater symptom severity(51). Reliability and validity has been assessed in multiple trials(52–54).

Small bowel bacterial overgrowth—The symptoms include bloating, nausea, vomiting, abdominal pain, diarrhea (with pale, greasy, voluminous, foul-smelling stools), excessive flatulence, and inability to gain or maintain body weight with good oral intake; the symptoms overlap with that of gastroparesis.

Proposed inclusion criteria for small bowel bacterial overgrowth

1. Symptoms of distention/bloating with or without diarrhea present for at least 3 of last 7 days
2. Abnormal glucose breath test
3. Plan to initiate antibiotics to assess sensitivity to change

Outcome measures administered at baseline and 4 weeks: Daily rating on Likert scale (55) for abdominal pain, distention, and diarrhea with 0 indicating not at all; 1, hardly; 2, somewhat; 3, moderately; 4, a good deal; 5, a great deal; and 6, a very great deal and the UCLA SCTC GIT 2.0(5). Daily rating scale was shown to be feasible, valid, and sensitivity to change in a recent large RCT (55).

Constipation—Colonic contractions are usually reduced or absent in patients with SSc, resulting in prolonged colonic transit (56) and symptoms of constipation.

Proposed inclusion criteria for constipation

1. Symptoms of constipation (having a bowel movement fewer than three times per week with usually hard, dry, small stools AND/OR painful bowel movement with straining during bowel movement) present for at least 3 of 7 last days
2. Slow transit constipation using Smart Pill® or radio opaque markers
3. Plan to initiate laxatives and/or fibers to assess sensitivity to change

Outcome measures administered at baseline and 12 weeks: Proportion of 3 or more complete spontaneous bowel movements (CSBMs) per week and an increase of one or more CSBMs from baseline during at least 9 of the 12 weeks(57); UCLA SCTC GIT 2.0(5)

Rectal incontinence—The patients present with chronic diarrhea, fecal incontinence and rectal prolapse.

Proposed inclusion criteria for rectal incontinence

1. Symptoms of bowel incontinence in 3 of last 7 days
2. Abnormal anorectal manometry showing impaired internal sphincter function
3. Plan for intervention such as surgery, sacral nerve stimulation to assess sensitivity to change

Outcome measures administered at baseline and 12 weeks: Fecal Incontinence Quality of Life scale (FIQL)(35); UCLA SCTC GIT 2.0(5) Fecal incontinence quality of life scale includes 29 items and 4 multi-item scales (lifestyle, coping/behavior, depression/self

perception, embarrassment). All scales are scored from 1 to 4, with 1 indicating a lower functional status of quality of life. Scales are the mean to all items in the scale(58). The fecal incontinence quality of life scale has been found to have acceptable reliability and validity in various studies(59–62).

Conclusions

This review discusses the available modalities to measure response to therapeutics in SSc-GIT. Identification of the etiology of GIT symptomatology in SSc can be aided by the use of patient reported outcomes and malnutrition assessments, which may guide the ordering of imaging.

Acknowledgments

Dr. Khanna was supported by the NIH/NIAMS K24 AR063120

References

1. Gyger G, Baron M. Gastrointestinal manifestations of scleroderma: recent progress in evaluation, pathogenesis, and management. Current rheumatology reports. 2012 Feb; 14(1):22–9. [Review]. [PubMed: 22105546]
2. Sjogren RW. Gastrointestinal features of scleroderma. Current opinion in rheumatology. 1996 Nov; 8(6):569–75. [Review]. [PubMed: 9018461]
3. Howe S, Eaker EY, Sallustio JE, Peebles C, Tan EM, Williams RC Jr. Antimyenteric neuronal antibodies in scleroderma. The Journal of clinical investigation. 1994 Aug; 94(2):761–70. [Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S.]. [PubMed: 8040331]
4. Kawaguchi Y, Nakamura Y, Matsumoto I, Nishimagi E, Satoh T, Kuwana M, et al. Muscarinic-3 acetylcholine receptor autoantibody in patients with systemic sclerosis: contribution to severe gastrointestinal tract dysmotility. Annals of the rheumatic diseases. 2009 May; 68(5):710–4. [Research Support, Non-U.S. Gov't]. [PubMed: 18762475]
5. Khanna D, Furst DE, Maranian P, Seibold JR, Impens A, Mayes MD, et al. Minimally important differences of the UCLA Scleroderma Clinical Trial Consortium Gastrointestinal Tract Instrument. The Journal of rheumatology. 2011 Sep; 38(9):1920–4. [Multicenter Study Randomized Controlled Trial Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't]. [PubMed: 21724699]
6. Khanna D, Hays RD, Maranian P, Seibold JR, Impens A, Mayes MD, et al. Reliability and validity of the University of California, Los Angeles Scleroderma Clinical Trial Consortium Gastrointestinal Tract Instrument. Arthritis Rheum. 2009 Sep 15; 61(9):1257–63. [PubMed: 19714600]
7. Bae S, Allanore Y, Coustet B, Maranian P, Khanna D. Development and validation of French version of the UCLA Scleroderma Clinical Trial Consortium Gastrointestinal Tract Instrument. Clinical and experimental rheumatology. 2011 Mar-Apr;29(2 Suppl 65):S15–21. [PubMed: 21586213]
8. Frech T, Hays RD, Maranian P, Clements PJ, Furst DE, Khanna D. Prevalence and correlates of sleep disturbance in systemic sclerosis--results from the UCLA scleroderma quality of life study. Rheumatology (Oxford). 2011 Jul; 50(7):1280–7. [PubMed: 21324979]
9. Baron M, Hudson M, Steele R, Lo E. Canadian Scleroderma Research G. Validation of the UCLA Scleroderma Clinica Trial Gastrointestinal Tract Instrument version 2.0 for systemic sclerosis. The Journal of rheumatology. 2011 Sep; 38(9):1925–30. [PubMed: 21724704]
10. Bodukam V, Hays RD, Maranian P, Furst DE, Seibold JR, Impens A, et al. Association of gastrointestinal involvement and depressive symptoms in patients with systemic sclerosis. Rheumatology (Oxford). 2011 Feb; 50(2):330–4. [PubMed: 20884655]
11. Hays RD, Hadorn D. Responsiveness to change: an aspect of validity, not a separate dimension. Quality of life research: an international journal of quality of life aspects of treatment, care and rehabilitation. 1992 Feb; 1(1):73–5.

12. Khanna D, Furst DE, Clements PJ, Park GS, Hays RD, Yoon J, et al. Responsiveness of the SF-36 and the Health Assessment Questionnaire Disability Index in a systemic sclerosis clinical trial. The Journal of rheumatology. 2005 May; 32(5):832–40. [PubMed: 15868618]
13. Pope J. Measures of systemic sclerosis (scleroderma): Health Assessment Questionnaire (HAQ) and Scleroderma HAQ (SHAQ), physician- and patient-rated global assessments, Symptom Burden Index (SBI), University of California, Los Angeles, Scleroderma Clinical Trials Consortium Gastrointestinal Scale (UCLA SCTC GIT) 2.0, Baseline Dyspnea Index (BDI) and Transition Dyspnea Index (TDI) (Mahler's Index), Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR), and Raynaud's Condition Score (RCS). Arthritis care & research. 2011 Nov; 63(Suppl 11):S98–111. [PubMed: 22588774]
14. Bae S, Allanore Y, Furst DE, Bodukam V, Coustet B, Morgaceva O, et al. Associations between a scleroderma-specific gastrointestinal instrument and objective tests of upper gastrointestinal involvements in systemic sclerosis. Clinical and experimental rheumatology. 2013 (In Press).
15. Frech TM, Khanna D, Maranian P, Frech EJ, Sawitzke AD, Murtaugh MA. Probiotics for the treatment of systemic sclerosis-associated gastrointestinal bloating/distention. Clinical and experimental rheumatology. 2011 Mar-Apr;29(2 Suppl 65):S22–5. [PubMed: 21586214]
16. Caporali R, Caccialanza R, Bonino C, Klersy C, Cereda E, Xoxi B, et al. Disease-related malnutrition in outpatients with systemic sclerosis. Clin Nutr. 2012 Oct; 31(5):666–71. [PubMed: 22417677]
17. Recasens MA, Puig C, Ortiz-Santamaria V. Nutrition in systemic sclerosis. Reumatologia clinica [Review]. 2012 May-Jun;8(3):135–40.
18. Baron M, Bernier P, Cote LF, Delegge MH, Falovitch G, Friedman G, et al. Screening and therapy for malnutrition and related gastro-intestinal disorders in systemic sclerosis: recommendations of a North American expert panel. Clinical and experimental rheumatology. 2010 Mar-Apr;28(2 Suppl 58):S42–6. [Multicenter Study Practice Guideline Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't]. [PubMed: 20576213]
19. Baron M, Hudson M, Steele R. Is serum albumin a marker of malnutrition in chronic disease? The scleroderma paradigm. Journal of the American College of Nutrition. 2010 Apr; 29(2):144–51. [Multicenter Study Research Support, Non-U.S. Gov't]. [PubMed: 20679150]
20. Murtaugh MA, Frech TM. Nutritional status and gastrointestinal symptoms in systemic sclerosis patients. Clin Nutr. 2013 Feb; 32(1):130–5. [Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't]. [PubMed: 22770637]
21. Harrison E, Herrick AL, McLaughlin JT, Lal S. Malnutrition in systemic sclerosis. Rheumatology (Oxford). 2012 Oct; 51(10):1747–56. [Research Support, Non-U.S. Gov't Review]. [PubMed: 22850183]
22. Godfrey K. Implementation of the Malnutrition Universal Screening Tool. Nursing times. 2004 May 4–10.100(18):61. [PubMed: 15151011]
23. Detsky AS, McLaughlin JR, Baker JP, Johnston N, Whittaker S, Mendelson RA, et al. What is subjective global assessment of nutritional status? JPEN Journal of parenteral and enteral nutrition. 1987 Jan-Feb;11(1):8–13. [Research Support, Non-U.S. Gov't]. [PubMed: 3820522]
24. Khanna D, Krishnan E, Dewitt EM, Khanna PP, Spiegel B, Hays RD. Patient-Reported Outcomes Measurement Information System (PROMIS(R)) -- The future of measuring patient reported outcomes in rheumatology. Arthritis care & research. 2011 Nov 1; 63(S11):S486–S90.
25. Forbes A, Marie I. Gastrointestinal complications: the most frequent internal complications of systemic sclerosis. Rheumatology (Oxford). 2009 Jun; 48(Suppl 3):iii36–9. [Research Support, Non-U.S. Gov't Review]. [PubMed: 19487222]
26. Raghu G, Freudenberger TD, Yang S, Curtis JR, Spada C, Hayes J, et al. High prevalence of abnormal acid gastro-oesophageal reflux in idiopathic pulmonary fibrosis. The European respiratory journal: official journal of the European Society for Clinical Respiratory Physiology. 2006 Jan; 27(1):136–42.
27. Gullung JL, Hill EG, Castell DO, Martin-Harris B. Oropharyngeal and esophageal swallowing impairments: their association and the predictive value of the modified barium swallow impairment profile and combined multichannel intraluminal impedance-esophageal manometry. The Annals of otology, rhinology, and laryngology. 2012 Nov; 121(11):738–45.

28. Logemann JA. Clinical efficacy and randomized clinical trials in dysphagia. International journal of speech-language pathology. 2012 Oct; 14(5):443–6. [Comment]. [PubMed: 22943582]
29. Beaumont H, Boeckxstaens G. Recent developments in esophageal motor disorders. Current opinion in gastroenterology. 2007 Jul; 23(4):416–21. [Review]. [PubMed: 17545779]
30. Chiou WK, Huang DH, Wang MH, Lee YJ, Lin JD. Significance and association of serum uric acid (UA) levels with components of metabolic syndrome (MS) in the elderly. Archives of gerontology and geriatrics. 2012 Nov-Dec;55(3):724–8. [PubMed: 22483588]
31. Condino AA, Sondheimer J, Pan Z, Gralla J, Perry D, O'Connor JA. Evaluation of infantile acid and nonacid gastroesophageal reflux using combined pH monitoring and impedance measurement. Journal of pediatric gastroenterology and nutrition. 2006 Jan; 42(1):16–21. [Evaluation Studies Research Support, N.I.H., Extramural]. [PubMed: 16385248]
32. Wang YT, Yazaki E, Sifrim D. High-resolution Manometry: Esophageal Disorders Not Addressed by the "Chicago Classification". Journal of neurogastroenterology and motility. 2012 Oct; 18(4): 365–72. [PubMed: 23105996]
33. Woodland P, Sifrim D. Management of gastro-oesophageal reflux disease symptoms that do not respond to proton pump inhibitors. Current opinion in gastroenterology. 2013 Apr 1.
34. Zhang X, Watson DI, Lally C, Bessell JR. Endoscopic ultrasound for preoperative staging of esophageal carcinoma. Surgical endoscopy. 2005 Dec; 19(12):1618–21. [PubMed: 16211436]
35. Neumann H, Fry LC, Neurath MF. Review article on current applications and future concepts of capsule endoscopy. Digestion. 2013; 87(2):91–9. [PubMed: 23306733]
36. Pandey AK, Wilcox P, Mayo JR, Moss R, Ellis J, Brown J, et al. Oesophageal dilatation on high-resolution CT chest in systemic sclerosis: what does it signify? Journal of medical imaging and radiation oncology. 2011 Dec; 55(6):551–5. [PubMed: 22141601]
37. de Geus-Oei LF, Vriens D, Arens AI, Hutchings M, Oyen WJ. FDG-PET/CT based response-adapted treatment. Cancer imaging: the official publication of the International Cancer Imaging Society. 2012; 12(2):324–35. [Review]. [PubMed: 23023063]
38. Pasha SF, Leighton JA. Endoscopic techniques for small bowel imaging. Radiologic clinics of North America. 2013 Jan; 51(1):177–87. [Review]. [PubMed: 23182515]
39. Solem CA, Loftus EV Jr, Fletcher JG, Baron TH, Gostout CJ, Petersen BT, et al. Small-bowel imaging in Crohn's disease: a prospective, blinded, 4-way comparison trial. Gastrointestinal endoscopy. 2008 Aug; 68(2):255–66. [Clinical Trial Comparative Study Research Support, Non-U.S. Gov't]. [PubMed: 18513722]
40. Hayakawa K, Tanikake M, Yoshida S, Urata Y, Inada Y, Narumi Y, et al. Radiological diagnosis of large-bowel obstruction: nonneoplastic etiology. Japanese journal of radiology. 2012 Aug; 30(7):541–52. [Review]. [PubMed: 22744438]
41. Mahieu P, Pringot J, Bodart P. Defecography: II. Contribution to the diagnosis of defecation disorders. Gastrointestinal radiology. 1984; 9(3):253–61. [PubMed: 6468863]
42. Balbir-Gurman A, Brook OR, Chermesh I, Braun-Moscovici Y. Pneumatosis cystoides intestinalis in scleroderma-related conditions. Internal medicine journal. 2012 Mar; 42(3):323–9. [Case Reports Review]. [PubMed: 22432985]
43. Weinstein, WKB. The gastrointestinal involvement in systemic sclerosis. Clemets, PJFD., editor. Philadelphia: Lippincott Williams and Wilkins; 2004.
44. Kahrilas PJ, Jonsson A, Denison H, Wernersson B, Hughes N, Howden CW. Concomitant Symptoms Itemized in the Reflux Disease Questionnaire Are Associated With Attenuated Heartburn Response to Acid Suppression. The American journal of gastroenterology. 2012 Jul 10.
45. Sawaya RA, Macgill A, Parkman HP, Friedenberg FK. Use of the Montreal global definition as an assessment of quality of life in reflux disease. Diseases of the esophagus: official journal of the International Society for Diseases of the Esophagus/ISDE. 2012 Aug; 25(6):477–83.
46. Kulich KR, Wiklund I, Junghard O. Factor structure of the Quality of Life in Reflux and Dyspepsia (QOLRAD) questionnaire evaluated in patients with heartburn predominant reflux disease. Quality of life research: an international journal of quality of life aspects of treatment, care and rehabilitation. 2003 Sep; 12(6):699–708. [Comparative Study].
47. Kulich KR, Madisch A, Pacini F, Pique JM, Regula J, Van Rensburg CJ, et al. Reliability and validity of the Gastrointestinal Symptom Rating Scale (GSRS) and Quality of Life in Reflux and

Dyspepsia (QOLRAD) questionnaire in dyspepsia: a six-country study. Health and quality of life outcomes. 2008; 6:12. [Research Support, Non-U.S. Gov't Validation Studies]. [PubMed: 18237386]

48. Wiklund IK, Junghard O, Grace E, Talley NJ, Kamm M, Veldhuyzen van Zanten S, et al. Quality of Life in Reflux and Dyspepsia patients. Psychometric documentation of a new disease-specific questionnaire (QOLRAD). The European journal of surgery Supplement: = Acta chirurgica Supplement. 1998; (583):41–9. [PubMed: 10027672]
49. Shaw M, Dent J, Beebe T, Junghard O, Wiklund I, Lind T, et al. The Reflux Disease Questionnaire: a measure for assessment of treatment response in clinical trials. Health and quality of life outcomes. 2008; 6:31. [Multicenter Study Randomized Controlled Trial Validation Studies]. [PubMed: 18447946]
50. Shaw MJ, Talley NJ, Beebe TJ, Rockwood T, Carlsson R, Adlis S, et al. Initial validation of a diagnostic questionnaire for gastroesophageal reflux disease. The American journal of gastroenterology. 2001 Jan; 96(1):52–7. [Validation Studies]. [PubMed: 11197287]
51. Revicki DA, Rentz AM, Dubois D, Kahrilas P, Stanghellini V, Talley NJ, et al. Gastroparesis Cardinal Symptom Index (GCSI): development and validation of a patient reported assessment of severity of gastroparesis symptoms. Quality of life research: an international journal of quality of life aspects of treatment, care and rehabilitation [Comparative Study Validation Studies]. 2004 May; 13(4):833–44.
52. Revicki DA, Camilleri M, Kuo B, Szarka LA, McCormack J, Parkman HP. Evaluating symptom outcomes in gastroparesis clinical trials: validity and responsiveness of the Gastroparesis Cardinal Symptom Index-Daily Diary (GCSI-DD). Neurogastroenterology and motility: the official journal of the European Gastrointestinal Motility Society. 2012 May; 24(5):456–63. e215–6. [Research Support, Non-U.S. Gov't]. [PubMed: 22284754]
53. Cassilly DW, Wang YR, Friedenberg FK, Nelson DB, Maurer AH, Parkman HP. Symptoms of gastroparesis: use of the gastroparesis cardinal symptom index in symptomatic patients referred for gastric emptying scintigraphy. Digestion. 2008; 78(2–3):144–51. [PubMed: 19033686]
54. Samuels N, Oberbaum M, Singer SR, Rony RY. Validation of a Hebrew translation of the Gastroparesis Cardinal Symptom Index (GCSI). Harefuah. 2010 Feb; 149(2):83–6. 125. [PubMed: 20549923]
55. Pimentel M, Lembo A, Chey WD, Zakko S, Ringel Y, Yu J, et al. Rifaximin therapy for patients with irritable bowel syndrome without constipation. The New England journal of medicine. 2011 Jan 6; 364(1):22–32. [Clinical Trial, Phase III Multicenter Study Randomized Controlled Trial Research Support, Non-U.S. Gov't]. [PubMed: 21208106]
56. Sallam H, McNearney TA, Chen JD. Systematic review: pathophysiology and management of gastrointestinal dysmotility in systemic sclerosis (scleroderma). Alimentary pharmacology & therapeutics. 2006 Mar 15; 23(6):691–712. [Research Support, Non-U.S. Gov't Review]. [PubMed: 16556171]
57. Lembo AJ, Schneier HA, Shiff SJ, Kurtz CB, MacDougall JE, Jia XD, et al. Two randomized trials of linaclotide for chronic constipation. The New England journal of medicine. 2011 Aug 11; 365(6):527–36. [Clinical Trial, Phase III Multicenter Study Randomized Controlled Trial Research Support, Non-U.S. Gov't]. [PubMed: 21830967]
58. Rockwood TH, Church JM, Fleshman JW, Kane RL, Mavrantonis C, Thorson AG, et al. Fecal Incontinence Quality of Life Scale: quality of life instrument for patients with fecal incontinence. Diseases of the colon and rectum. 2000 Jan; 43(1):9–16. [Multicenter Study Research Support, Non-U.S. Gov't]. discussion -7. [PubMed: 10813117]
59. Rockwood TH. Incontinence severity and QOL scales for fecal incontinence. Gastroenterology. 2004 Jan; 126(1 Suppl 1):S106–13. [Review]. [PubMed: 14978646]
60. Ahnis A, Holzhausen M, Rockwood TH, Rosemeier HP. FLQAI - A Questionnaire on Quality of Life in Fecal Incontinence: German translation and validation of Rockwood et al.'s (2000) Fecal Incontinence Quality of Life Scale (FIQLS). Zeitschrift fur Gastroenterologie. 2012 Jul; 50(7): 661–9. [Research Support, Non-U.S. Gov't]. [PubMed: 22760677]
61. Bordeianou L, Lee KY, Rockwood T, Baxter NN, Lowry A, Mellgren A, et al. Anal resting pressures at manometry correlate with the Fecal Incontinence Severity Index and with presence of

sphincter defects on ultrasound. Diseases of the colon and rectum. 2008 Jul; 51(7):1010–4. [Comparative Study]. [PubMed: 18437494]

62. Reilly WT, Talley NJ, Pemberton JH, Zinsmeister AR. Validation of a questionnaire to assess fecal incontinence and associated risk factors: Fecal Incontinence Questionnaire. Diseases of the colon and rectum. 2000 Feb; 43(2):146–53. [Comparative Study]. discussion 53–4. [PubMed: 10696886]

3–5 key points

GIT is a common cause of morbidity and has negative impact on quality of life in SSc.

There is dearth of clinical trials in SSc-GIT due to lack of feasible outcome measures.

Recent evidence supports feasibility, reliability, and validity of UCLA SCTC GIT 2.0 in SSc-GIT as an outcome measure.

Recommendations are provided to validate outcome measures in GIT-associated gastro-esophageal reflux disease, gastroparesis, small bowel bacterial overgrowth, constipation, and rectal incontinence.

Table 1

Investigational modalities to assess gastrointestinal motility and mucosal involvement

	Esophagus	**Stomach**	**Small bowel**	**Large bowel**	**Anorectum**
Motility	Modified barium swallow	Scintigraphy	Manometry	Radio-opaque markers	Manometry
	Manometry	Antro-duodenal manometry	Scintigraphy	Scintigraphy	Endo-sonography
	Impedance monitoring	Electro-gastrography	Lactulose breath test	Wireless motility capsule¶	High resolution manometry¶
	Combined impedance and manometry	Gastric emptying breath test	Wireless motility capsule¶	MRI¶	Surface electro-myography¶
	Esophageal pH monitoring	Single photon emission computerized tomography	MRI¶ and dynamic MRI¶	Manometry¶	Dynamic MRI¶
	Scintigraphy	Wireless pH monitoring			Defecography¶
	High resolution manometry¶	Magnetic resonance imaging (MRI) ¶			Balloon expulsion test¶
	Wireless pH monitoring¶				
	pH-impedancemetry¶				
Mucosal involvement	Endoscopy	Endoscopy	Enteroscopy (Balloon assisted and spiral)	Colonoscopy	Colonoscopy
	Endoscopic ultrasound	Endoscopic ultrasound	Capsule Endoscopy		
	Capsule endoscopy	Capsule endoscopy			

¶ Not studied in SSc

Table 2

Patient-reported GIT severity as assessed by the UCLA SCTC GIT 2.0

Scales	None-to-Mild	Moderate	Severe-to Very Severe
Reflux	0.00–0.49	0.50–1.00	1.01–3.00
Distention/Bloating	0.00–1.00	1.01–1.60	1.61–3.00
Diarrhea	0.00–0.49	0.50–1.00	1.01–2.00
Constipation	0.00–0.49	0.50–1.00	1.01–3.00
Fecal Soilage	0.00–1.00	1.01–2.00	2.01–2.50
Emotional Weil-Being	0.00–0.49	0.50–1.00	1.01–3.00
Social Functioning	0.00–0.49	0.50–1.00	1.01–3.00
Total GIT score	0.00–0.49	0.50–1.00	1.01–3.00