Title

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Authors

McMahan, Zsuzsanna
Tucker, Ana
Perin, Jamie
et al.

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The relationship between gastrointestinal transit, Medsger GI severity, and UCLA GIT 2.0 symptoms in patients with systemic sclerosis

Zsuzsanna H. McMahan, MD, MHS[1], **Ana E. Tucker, MD**[2], **Jamie Perin, PhD, MS**[3], **Elizabeth R. Volkmann, MD, MS**[4], **Subhash Kulkarni, PhD, MS**[5], **Harvey A. Ziessman, MD**[6], **Pankaj J. Pasricha, MBBS, MD**[5], **Fredrick M. Wigley, MD**[1]

[1]Johns Hopkins University, Division of Rheumatology

[2]Johns Hopkins Bayview, Department of Internal Medicine

[3]Johns Hopkins Bloomberg School of Public Health, Department of International Health

[4]University of California- Los Angeles, Division of Rheumatology

[5]Johns Hopkins University, Division of Gastroenterology

[6]Johns Hopkins University, Department of Radiology

Abstract

Objective: Scleroderma (SSc)-associated gastrointestinal (GI) complications are attributed to a variety of factors including diet, microbiota dysbiosis, or GI transit abnormalities. We examined the contribution of abnormal GI transit to SSc Medsger GI severity scores and/or UCLA GIT 2.0 symptoms.

Methods: Patients with SSc and GI symptoms (n=71) and healthy controls (n=18) underwent whole gut transit (WGT) scintigraphy to assess transit from the esophagus to the colon. The presence of delayed transit and percent emptying in each GI region were measured. We compared the WGT measurements between categories of the Medsger GI severity score (0–4) and across UCLA GIT 2.0 domains and total score (0–3).

Results: Eighty-percent of patients had >1 abnormal region of the gut on WGT scintigraphy. All patients requiring total parenteral nutrition had delayed small bowel transit, compared to only ~11% of patients in other Medsger GI severity groups (p=<0.01). Severe colonic transit delays were more likely in patients with Medsger GI scores of 3 (pseudo-obstruction and/or malabsorption) compared to other Medsger GI groups (p=0.02). Seventy-percent of these patients had ≤30% colonic emptying at 72 hours. Modest associations were noted between GERD symptoms and delayed esophageal (r=−0.31,p=0.05) and gastric emptying (r=−0.32,p=0.05).

Corresponding author: Zsuzsanna McMahan, MD, MHS, 5200 Eastern Avenue, Suite 5200, Mason F. Lord Building, Center Tower, Baltimore, MD 21224, Tel: 410-550-2003; Fax: 410-550-2072, zmcmaha1@jhmi.edu.

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Conclusion: These data are important in providing evidence that SSc bowel disease affects transit of GI content and that delay in transit accounts in part for both bowel symptoms and Medsger GI severity. Prospective studies examining the benefit of early therapeutic intervention targeting GI transit abnormalities in patients at high-risk for severe GI complications are needed.

Keywords

systemic sclerosis; scleroderma; whole gut scintigraphy; gastrointestinal; gastrointestinal tract

INTRODUCTION

Systemic sclerosis (SSc) is a complex disease characterized by autoimmunity, progressive vasculopathy, and excess deposition of collagen due to aberrant fibroblast function in the skin and internal organs. (1,2) The gastrointestinal (GI) tract is the most commonly identified internal organ involved in SSc, with approximately 90% of patients affected. (3) GI manifestations in patients with SSc are variable in terms of symptoms, complications, time course, and region(s) affected. (4,5) A number of factors may contribute to GI symptoms and severity including diet, microbiota dysbiosis, or abnormalities in GI transit. (6,7) Pathological findings and previous physiological studies implicate bowel dysfunction leading to dysmotility, yet these studies have not clearly determined the clinical impact of abnormalities in GI transit of food or content, particularly in the lower bowel. (8–12) Understanding the relationship between GI severity, symptoms, and abnormal GI transit may allow for a more targeted approach in the management of such patients with regards to the selection and application of distinct therapies (13–16). For example, some medications, such as octreotide, primarily impact small bowel motility, whereas others like prucalopride or linaclotide have a more significant impact on large bowel motility. (17–19)

Whole gut transit scintigraphy is a tool used to objectively assess GI transit from the esophagus to the colon. It utilizes the passage of radioisotopes ingested as a solid and liquid meal through the gut to determine the extent and severity of the transit abnormalities. (20) The results of WGT scintigraphy can help accurately define the regions of the gut affected by dysmotility as well as categorize transit severity. (14)

We hypothesize that abnormal GI transit will associate with the severity of bowel dysfunction and specific GI clinical complaints. We utilized WGT studies in conjunction with the Medsger GI severity score and UCLA Scleroderma Clinical Trial Consortium (SCTC) GIT 2.0 instrument to evaluate these associations. (21–23) Identifying such GI abnormalities that associate with poor outcomes would facilitate the application of targeted therapies and the study of earlier initiation of GI interventions in high-risk subgroups.

PATIENTS AND METHODS

Patients.

All patients were from the Johns Hopkins Scleroderma Center and met the 2013 American College of Rheumatology/European League Against Rheumatism criteria for systemic sclerosis. (24) Patients were part of a prospectively enrolled GI cohort of patients evaluated

in the Johns Hopkins Scleroderma Center (GI Assessment Protocol cohort, or GAP). Whole gut scintigraphy studies were obtained as part of clinical care in patients who had symptoms of significant upper GI disease or symptoms of both lower and upper GI dysfunction. At the clinical visit, significant symptoms of GI dysfunction were defined as early satiety, nausea/vomiting, unintentional weight loss, distension, bloating, diarrhea, and/or constipation as determined by the treating physician. In order to include patients from across the spectrum of GI disease, WGT studies on minimally symptomatic (e.g. mild heartburn alone) or asymptomatic SSc patients were obtained as part of a research protocol. All study patients were evaluated during their routine clinical visits at the Johns Hopkins Scleroderma Center. Written informed consent was obtained from all patients. The present study was approved by the Johns Hopkins Institutional Review Board.

Clinical Phenotyping of the SSc patients.

The Johns Hopkins Scleroderma Center database collects demographic and detailed clinical data from patients at their first clinical encounter and every 6 months at subsequent follow-up clinical visits. Age and disease duration were calculated from the date of birth and the date of the first SSc-associated symptom (Raynaud's or non-Raynaud's) to the date of the WGT study, respectively. Patients were identified as having limited or diffuse SSc based on the extent of skin tightness. (25) To define SSc phenotypes associated with specific GI dysmotility patterns and GI severity, the maximum clinical severity scores were utilized. The presence of a myopathy was denoted on the basis of: an elevated creatine phosphokinase with evidence of electromyography (EMG) supportive of myopathy, magnetic resonance imaging (MRI) with evidence of muscle edema, or muscle biopsy consistent with myopathy. (22) The muscle severity score was also used to classify the degree of associated proximal muscle weakness and was based on the following scale collected in our database: 0=full strength, 1 = ability to lift upper or lower extremities against gravity with some resistance, 2 = ability to lift upper or lower extremities against gravity only, 3= ability to move upper or lower extremities but not against gravity, and 4= requiring ambulatory aids to walk. (22,26) Cardiac involvement was determined by the Medsger severity scale and was considered present with a score of 1 or greater [0 = normal, 1 = evidence of conduction defect on electrocardiogram or left ventricular ejection fraction (LVEF) of 45–49% on echocardiogram, 2= evidence of arrhythmia on electrocardiogram or LVEF of 40–44%, 3= clinical signs of left or right heart failure or arrhythmia requiring treatment with medication or intervention]. (22,26) To capture the clinical phenotype, the minimum measurements from the forced vital capacity (FVC) and single breath diffusing capacity of carbon monoxide (DLCO) pulmonary lung function testing and maximum measurements from the estimated right ventricular systolic pressure (RVSP) (measured by transthoracic echocardiogram) were utilized for the analysis. (27) Sicca symptoms were defined as the presence of at least one of the following: dry eyes for more than three months, the use of artificial tears three times daily, dry mouth for more than three months, swollen salivary glands, the necessity of liquids for swallowing due to dry mouth, and/or the sensation of sand or gravel in one's eyes. (28) Evidence of patient-reported GI symptoms was determined by the UCLA GIT 2.0 survey from the time closest to the WGT study.

Autoantibody Profile.

SSc autoantibodies (Scl-70, centromere, RNA polymerase III) were determined for patients with available serum using a commercially available Euroline immunoblot assay [Scleroderma (Nucleoli) Profile Euroline IgG); Euroimmun]. Moderate to high-titers of autoantibodies, as determined by the manufacturer's cutoffs, were considered positive.

Control population.

The control population of 18 patients with WGT studies was obtained from Johns Hopkins Nuclear Medicine. These individuals were recruited through in-house advertisements and were interviewed and screened with the aid of the Mayo Clinic Research Questionnaire. The accepted controls had no history of gastrointestinal disorders or prior surgery, were not taking any medications, did not smoke or abuse alcohol (no more than 2–3 drinks per week) and were screened for GI disease through a standard questionnaire. Individuals without a history or symptoms of GI disease were enrolled in this cohort. (29)

Instruments.

The UCLA SCTC GIT 2.0 instrument. Each scale has a weighted sub-score, with a 3-point categorical response (0–3) used to evaluate all items, excluding items 15 and 31 in the diarrhea and constipation categories, respectively, which rely on a score of zero or one.

Modified Medsger GI Severity Score. Physician-reported GI symptom severity was classified using the modified Medsger severity score. (22) The score is composed of five categories which include: (a) score 0 = normal (no GI symptoms); (b) score 1 = requiring GERD medications, including an H2 blocker, proton pump inhibitor or pro-kinetic, or an abnormal bowel series; (c) score 2 = requiring high dose GERD meds (defined as greater than the lowest daily dose or a proton pump inhibitor plus a pro-kinetic drug) and/or having small bowel dilation on radiography; (d) score 3 = episodes of pseudo-obstruction or malabsorption syndrome; and (e) score 4 = severe GI dysmotility requiring either supplemental enteral or total parenteral nutrition (TPN).

Whole gut transit study. Upon study entry, whole-gut transit scintigraphy was obtained in all patients. Three days prior to the study, patients were instructed to refrain from taking promotility agents, stool softeners, opiates, benzodiazepines, or antibiotics (Supplemental Table 1). Patients were instructed to begin fasting at midnight prior to the study. WGT scintigraphy required that the patient consume a standard amount of radiolabeled In-111 water for the esophageal portion and the liquid gastric emptying parts of the study. The patient then consumed a radiolabeled Tc-99m standard egg meal as part of the solid gastric emptying study. Anterior and posterior standing images were obtained by a gamma camera at standard times [1 hour (hr), 2 hr, 4 hr, 6 hr, 24 hr, 48 hr, and 72 hrs] to track the transit of meals through the esophagus, stomach, small and large intestines. Gamma cameras were placed at the front and back of the patient to monitor counts of radiation. A standard validated formula (geometric mean) was used to correct for soft tissue attenuation. Transit and emptying times were measured for each anatomic region of the gut. The standardized ranges of normal and abnormal transit, percent emptying at a given time in each region, and continuous transit times in controls were described previously. (29,30)

Statistical Methods.

Cross-sectional analysis.—We first sought to compare the clinical and demographic features of patients in the GAP cohort with patients in the Johns Hopkins Scleroderma Center cohort to determine whether the GAP cohort is representative overall of the scleroderma patients seen in our Center. We performed Chi-square or Fischer's exact tests to evaluate for associations between dichotomous clinical and demographic variables.

We then sought to determine whether physician-scored GI clinical severity as measured by the Medsger severity score (e.g. pseudo-obstruction/malabsorption, TPN dependence, etc.) is related to the presence of abnormal transit in distinct anatomical GI regions or to the extent of GI transit delays. We described WGT transit study data within each category of Medsger GI severity using both the dichotomous (presence or absence of dysmotility) and continuous data (percent emptying in an anatomical region and transit time). To determine whether GI symptoms associated with specific GI transit abnormalities, we estimated the association between GI symptom scores (i.e. reflux, distention, diarrhea, etc.) of the UCLA GIT 2.0 and continuous measures of GI transit from the WGT studies using Spearman's rank correlations. We performed Fischer's exact tests to assess for the proportion of abnormal transit by region (e.g. esophagus, stomach, small bowel, and colon) in each category of the Medsger GI severity score. We also calculated the median (interquartile range; IQR) for regional transit using the Medsger GI score, and compared the transit times of each region (e.g. esophagus) for a trend across Medsger severity categories using linear regression. Pearson correlations were estimated for continuous variables, and Spearman correlations were estimated for highly skewed continuous variables. Student's t-tests were used to examine differences between the means of continuous variables between two groups.

STATA 15 (STATA Corporation, College Station, Texas) was used to perform the analyses. A p-value of ≤0.05 was considered statistically significant.

RESULTS

Clinical characteristics of the study cohort relative to other patients in the JHSC.

Between October 2014 and February 2019, 71 patients who met criteria for SSc with GI symptoms were evaluated at the Johns Hopkins Scleroderma Center and completed WGT scintigraphy and the UCLA GIT 2.0 survey (GAP cohort). Patient average (± SD) age with first manifestation of symptoms was 41 (± 14) years. Of these patients, 85.9% were female and 78.6% were Caucasian. The median (interquartile range) disease duration of SSc was 6.5 years (2.6 – 17.6 years), and mean body mass index (BMI) was 25.9 (± 7.3) kg/m^2. Limited cutaneous disease was present in 70% of patients. In the cohort, 18.2% of patients had evidence of cardiac involvement (Medsger cardiac score >1), and 54.6% had evidence of lung involvement (Medsger lung score >1). In addition, 14.1% of patients had evidence of myopathy, 41.8% had a Raynaud's severity score >1, and 71.6% had sicca symptoms. Table 1 summarizes the demographic features of the cohort.

During the same time period, 1,445 SSc patients were seen in our Center and did not enroll in this study. In order to determine if the study cohort was representative of the rest of the Scleroderma Center cohort, we compared clinical and serological characteristics between

these two groups. Patients in the study group were largely comparable to the patients in the SSc cohort, though patients in the study group had a longer disease duration (from onset of first symptoms to baseline visit [6.5 vs. 4.2 years; p<0.01]). In the study group there were fewer patients with mild GI disease (Medsger GI severity score of 1) [22.4% vs. 42.2%, p<0.01] and more patients with severe GI disease (Medsger GI severity score of 3) [14.9% vs. 5.5%, p<0.01]. In the study group, there was less severe Raynaud's [Medsger score ≥2 in 41.8% vs. 55.0%, p=0.03] and a better forced vital capacity [79.9% vs. 72.8%, p<0.01], which is to be expected in a cohort of patients with predominantly limited cutaneous disease. (31) Anti-centromere antibodies were more commonly present in our study cohort [45% vs. 27%, p<0.01], while anti-RNA polymerase III (anti-RNAP) antibodies were significantly less prevalent [3% vs. 17%, p<0.01]. Given that GI disease is known to be less severe among patients with anti-RNAP antibodies, as well as the higher prevalence of limited cutaneous disease in our cohort, these findings were not surprising. (32–35) The distribution of other clinical features and serologies were otherwise comparable between the two groups.

Gastrointestinal (GI) characteristics of the cohort

GI transit measured by whole gut scintigraphy is significantly different between SSc patients and controls.—As this was the first study to measure GI transit in SSc using WGT scintigraphy, we first compared transit times and percent emptying between patients with SSc and control patients. As expected, SSc patients had significantly higher prevalence of abnormal esophageal function than the control group [59% vs. 12%; p<0.01]. The median esophageal transit time was significantly delayed in SSc patients when compared to controls [22 seconds vs. 10 seconds; p<0.01], as was the median esophageal percentage emptying at 10 seconds [80% vs. 92%; p<0.01]. Gastric emptying as measured by the percent emptying of solids at both 2 hours [61% vs. 84%; p<0.01] and 4 hours [95% vs. 98%; p<0.01] was significantly delayed in SSc patients compared to controls. Delayed small bowel transit was more common among SSc patients compared to controls, though the number of abnormal studies was small, and the difference in the prevalence of this abnormality was not statistically significant [14% vs. 6%; p=0.45]. The percent colonic emptying at 72 hours was also significantly less in SSc patients compared to controls [48% vs. 84%; p=0.02]. Table 2 summarizes the whole gut scintigraphy findings in both cohorts.

Delayed GI transit in specific parts of the gut associates with severe SSc GI complications.—In order to determine whether specific GI transit abnormalities associate with specific clinical GI complications, we examined the prevalence of delayed transit in the esophagus, stomach, small bowel, and colon (measured by WGT) within each category of Medsger GI severity. We then compared transit times/percent emptying in the esophagus, stomach, small bowel, and colon across each category of the Medsger GI severity score (see Table 3).

The esophagus and colon were most frequently abnormal on WGT scintigraphy across all categories of the Medsger GI score. Evidence of delayed esophageal transit was noted in the majority of patients without symptoms (Medsger score 0) (~60%). (11) In patients with mild symptoms of GERD (Medsger 1), less than half had evidence of delayed esophageal transit. In contrast, more patients with refractory GERD (Medsger 2) had both delayed esophageal

transit and gastroparesis compared to patients in the Medsger 1 group, though the difference was not statistically significant.

Small bowel transit delay was rare among most Medsger GI severity groups (scores 0–3), as each of these Medsger GI groups had an estimated 11% of patients with evidence of small bowel transit delay. In contrast, among the most severe Medsger category of GI disease (Medsger 4; TPN dependence), 3/3 (100%) had small bowel involvement. Table 3 summarizes the association between the Medsger severity scores and WGT study findings.

Among patients scored as having recurrent pseudo-obstruction and malabsorption (Medsger GI score of 3), colonic transit was severely delayed with a median percent emptying of 3.5% at 72 hours on WGT, which was lower than the other groups collectively (p=0.02). In addition, within this group of patients, almost 1/3 (27%) had no colonic emptying (0%) at 72 hours, which was not the case for any other Medsger GI severity score. When looking across all groups of Medsger GI severity, by linear regression, we found that there was a trend toward more severe disease and lower percent colonic emptying at 72 hours (p=0.07). Finally, when comparing severe and none-to-moderate GI disease (Medsger 3 or 4 vs. 0–2, respectively), patients with more severe disease had a lower mean percent emptying of the colon at 72 hours compared to those with none-to-moderate disease (27% vs. 53%; p=0.04).

GI symptoms (GIT 2.0) associate with GI transit delays by WGT in SSc.—The median interval between the collection of the UCLA GIT 2.0 survey and the WGT study was −0.08 (−5.08, 8.75) months. Using the UCLA GIT 2.0 scale, greater reflux scores showed a modest association with longer esophageal transit time (r=0.27; p=0.05), slower percentage of esophageal emptying at 10 seconds (r=−0.31; p=0.05) and delayed gastric emptying at 3 hours (r=−0.34; p=0.05). Esophageal transit time was positively associated with GIT diarrhea scores (r= 0.37; p<0.05). Patient-reported symptoms of distention and bloating were inversely associated with percent gastric emptying at 3 hours (r=−0.27; p= 0.06) (Table 4). Gastric emptying at 3 hours was also inversely associated with a higher (more severe) total GIT score (r=−0.30; p<0.05) and a trend towards worse patient-reported social well-being (r=−0.26; p=0.06). However, symptoms determined by the constipation domain of the GIT did not show significant associations with objective findings of delayed colonic transit on WGT studies. Table 4 summarizes the correlation between WGT results and patient-reported symptoms as measured by the UCLA GIT 2.0 survey scores.

DISCUSSION

In this study, we sought to examine whether abnormal GI transit contributes to GI severity and symptoms in SSc. We found that patients with pseudo-obstruction and/or malabsorption syndrome are more likely to have severe colonic transit delays, with a third of such patients having almost no colonic emptying at 72 hours. We also determined that patients on TPN are significantly more likely to have small bowel involvement when compared to other Medsger GI severity groups. Patients with Medsger GI scores representative of more significant upper GI symptoms (Medsger GI score of 1 or 2) are more likely to have dysmotility of both the esophagus and/or stomach. These data are important in providing insight on the impact of

transit defects on SSc GI complications. Finally, we determined that patient symptoms as measured by the UCLA GIT 2.0 are associated with delayed transit.

In this study, small bowel involvement was significantly more prevalent among SSc patients with the most severe GI disease requiring TPN. Interestingly, these patients were not more likely than other groups to have gastroparesis, and were less likely than other groups to have delayed colonic transit. Though the number of patients was small in this analysis, the association highlights the importance of small bowel function in optimizing nutrition in SSc. Recognizing the high prevalence of small bowel transit delays in this group of patients with severe disease and a high morbidity and mortality also emphasizes the need for the earlier application of targeted clinical therapies that positively influence small bowel transit such as octreotide. (18)

The finding that severe colonic transit delays were more likely in patients with pseudo-obstruction (Medsger score 3) and/or malabsorption syndrome compared to other Medsger GI groups ($p=0.02$) is also interesting. The majority of patients in our study with pseudo-obstruction and/or malabsorption (70%) had ≤30% emptying of the colon at 72 hours (normal ≥ 67%) which is less than half of what would normally be expected. This finding reflects the importance of abnormal colonic motility in SSc, either as a marker of more generalized dysmotility or as a direct contributor to pseudo-obstruction via upstream reflexes. This is consistent with recent studies which showed that colonic dysfunction leads to significant morbidity and mortality in SSc and lends to the hypothesis that early treatment of patients with delayed colonic transit with pro-motility agents, such as prucalopride, may help prevent this complication. (36,37)

We also demonstrate that symptoms based on UCLA GIT 2.0 scores correlate with objective GI transit abnormalities in patients with SSc. We identified a moderate inverse association between UCLA GIT 2.0 GERD domain scores and esophageal transit times and gastric emptying. These findings bordered on statistical significance and were only modest, possibly because symptoms of heartburn, dysphagia, and regurgitation (captured in the GERD domain) in SSc may also be due to other causes such as a hypotensive LES or gastroparesis, neither of which would necessarily affect esophageal transit time. Thus, patients with highly symptomatic GERD may have normal esophageal transit. In addition, symptoms of distention and bloating were significantly associated with delayed gastric transit at 3 hours. These results were similar to prior studies that demonstrated association with epigastric fullness and prolonged gastric emptying. (38)

Finally, we also confirmed that SSc can affect several regions of the GI tract simultaneously, most commonly the esophagus and colon, and that a negative test in one region does not preclude abnormalities in other regions. Prior studies have demonstrated a high correlation between delayed gastric and esophageal emptying. (38,39) Furthermore, a significant correlation was noted between the rate of gastric emptying and abnormal esophageal transit values, suggesting that worsening severity could coexist and extend between regions. (38,39) These results suggest that delayed gastric emptying can lead to reflux and possible delay in esophageal transit. Determining early on whether symptoms of GERD are occurring

in the presence of significant gastric transit delays may lead to more effective symptom management (e.g. combining metoclopramide with a standard GERD regimen).

Our study has several strengths and limitations. This is the first study to assess whole gut transit in a large SSc population. The strengths of our study include evaluating WGT using a diverse cohort of well-characterized patients. We intentionally enriched our cohort with patients who had more severe GI disease so as to learn about the impact of abnormal transit on less frequently observed, but more severe SSc GI complications. We correlated the results of WGT studies with validated patient- and physician-reported outcome measures used to assess GI severity and symptoms of GI dysfunction. From the standpoint of limitations, there is a known lack of standardization in whole gut scintigraphy protocols and interpretation which may affect reliability of results when compared between centers. (40) The time interval between our symptom surveys and the WGT study also limits the interpretation of our findings, as a subset of surveys were collected retrospectively. Our study also did not address how disease modifying agents impact whole gut scintigraphy results in SSc patients, which may merit further investigation through future studies. Finally, we recognize that transit studies are only one measure of motility and may fail to capture dysmotility at either an earlier stage or in some other form (e.g. lack of gastric accommodation).

CONCLUSIONS

WGT studies revealed that delayed transit in the small bowel and colon are associated with more severe GI complications in SSc, as currently defined by the Medsger scale. However, GI dysmotility often involves more than one region of the gut in scleroderma, therefore more comprehensive testing may be indicated in symptomatic patients. WGT studies correlate well with the localization of symptoms in SSc (upper versus lower), and when combined with patient and physician-reported GI severity scores they may contribute to a more comprehensive approach in assessing severity of GI disease in SSc. Future studies examining the benefit of early therapeutic intervention targeting GI transit abnormalities in patients at high risk for severe GI complications are warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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SIGNIFICANCE AND INNOVATIONS

- Delayed GI transit in specific regions of the gut plays a role in severe GI complications in patients with scleroderma.
- Severe GI phenotypes in systemic sclerosis associate with delayed transit in the small bowel and colon on whole gut transit studies.
- Several regions of the GI tract in scleroderma patients may be affected by dysmotility simultaneously, the knowledge of which can impact our understanding and approach to targeted clinical therapies for scleroderma patients with GI disease.

Table 1.

Characteristics of the SSc patients with and without WGT in the Johns Hopkins Scleroderma Center cohort

Clinical and demographic features	WGT (n=71)	No WGT (n=1445)	p-value
Age at first symptoms, mean (SD)	41 (14)	42 (15)	0.59
Disease duration from 1st symptoms to baseline visit, median (IQR)	6.5 (2.6–17.6)	4.2 (1.6–11.8)	**<0.01**
Male sex, % (n)	14.1 (10/71)	15.4 (222/1442)	0.77
Body mass index (BMI), mean (SD)	25.9 ± 7.3	n/a	
Race/Ethnicity			
White, % (n)	78.6 (55/70)	76.1 (1097/1441)	0.64
Ever smoker, % (n)	11.3 (6/53)	10.5 (101/958)	0.86
SSc Type			
Limited cutaneous disease, % (n)	70.0 (49/70)	62.6 (891/1423)	0.25
Max GI score at their first visit, % (n)			
Medsger GI score 0	7.5 (5/67)	8.2 (118/1443)	1.00
Medsger GI score 1	22.4 (15/67)	42.2 (609/1443)	**<0.01**
Medsger GI score 2	50.8 (34/67)	42.6 (615/1443)	0.19
Medsger GI score 3	14.9 (10/67)	5.5 (80/1443)	**<0.01**
Medsger GI score 4	4.5 (3/67)	1.5 (21/1443)	0.09
Cardiac involvement (>1), % (n)	18.2 (10/55)	24.1 (318/1317)	0.31
Myopathy, % (n)	14.1 (9/64)	22.0 (314/1427)	0.13
Sicca, % (n)	71.6 (48/67)	70.7 (1019/1441)	0.87
Raynaud's severity (>1), % (n)	41.8 (28/67)	55.0 (794/1443)	**0.03**
Lung involvement (>1), % (n)	54.6 (30/55)	64 (837/1304)	0.15
Cancer, % (n)	23.2 (16/69)	17.7 (256/1445)	0.25
Dead, % (n)	2.9 (2/70)	8.2 (93/1132)	0.17
Pulmonary function parameters			
FVC, % predicted, mean (SD)	79.9 (23.0)	72.8 (19.9)	**<0.01**
DLCO, % predicted, mean (SD)	66.1 (26.4)	64.2 (23.7)	0.54
RVSP by echo (mmHg), mean (SD)	31.2 (6.8)	34.7 (19.1)	0.30
Antibodies, % (n)			
Scl70 (i.e. Topoisomerase-1)	16 (10/62)	25 (291/1162)	0.11
Centromere	45 (28/62)	27 (318/1162)	**<0.01**
RNA polymerase-3	3 (2/62)	17 (193/1162)	**<0.01**
Ro52	24 (15/62)	27 (308/1162)	0.69
ThTo	7 (4/62)	8 (91/1162)	1.00
U3RNP	5 (3/62)	7 (78/1162)	0.79
Ku	8 (5/62)	4 (45/1162)	0.10
PMScl	3 (2/62)	3 (32/1162)	0.70

Table 2.

Objective GI involvement in SSc using the whole gut transit study

Region of the gut	WGT in SSc (n=71)	WGT in controls (n=18)	P-value
Esophagus			
Abnormal, n (%)	41/70 (59)	2/17 (12)	**<0.01**
Esophageal Transit Time (sec), median (IQR)	22 (11–30)	10 (8–12)	**<0.01**
Esophageal % emptying at 10 sec, median (IQR)	80 (62–88)	92 (86–93)	**<0.01**
Stomach			
Liquid			
Abnormal, n (%)	16/71 (23)	1/18 (6)	0.18
Delayed T1/2 (min)	18 (13–22)	16 (11–20)	0.17
Solid			
Abnormal, n (%)	13/71 (18)	1/18 (6)	0.28
% emptying at 2 hours, median (IQR)	61 (45–75)	84 (65–87)	**<0.01**
% emptying at 4 hours, median (IQR)	95 (88–98)	98 (97–99)	**<0.01**
Small bowel			
Abnormal, n (%)	10/70 (14)	1/18 (6)	0.45
% emptying at 6 hours, median (IQR)	73 (58–82)	72 (62–77)	0.53
Colon			
Abnormal, n (%)	38/69 (55)	7/18 (39)	0.22
% emptying at 72 hours, median (IQR)	48 (0–87)	84 (60–94)	**0.02**

Normal ranges: Esophageal transit time (ETT) = >15 seconds; Esophageal emptying at 10 sec= ≥ 83%; Normal liquid T1/2 ≤ 74 min solid emptying 2 hrs ≥ 40%; solid emptying 4 hrs ≥ 90%; Normal small bowel transit time at 6 hrs ≥49%; Normal % colonic emptying at 72 hrs ≥ 67%

Table 3.

Association between whole gut transit study and Medsger severity scores

	Medsger 0	Medsger 1	Medsger 2	Medsger 3	Medsger 4	Significance	Normal values
Esophagus							
Abnormal, n (%)	3/5 (60%)	6/15 (40%)	19/33 (58%)	9/10 (90%)	2/3 (66%)	0.15 *	n/a
ETT (sec), median (IQR)	19 (14–29)	11 (9–30)	26 (11–30)	29 (16–30)	29 (4–30)	0.17	< 15 sec.
%emptying, median (IQR)	81% (77–89)	84% (62–90)	81% (64–88)	69% (56–84)	77% (77–90)	0.51	≥ 83%
Stomach							
Abnormal solid emptying, n (%)	0/5 (0%)	2/15 (13%)	7/34 (21%)	3/10 (30%)	0/3 (0%)	0.50 *	n/a
Liquid ½ time, median (IQR)	17 (15–17)	16 (13–21)	18 (12–22)	21 (18–58)	22 (12–34)	0.17 †	≤ 25 min.
% Solid 2 hours, median (IQR)	53% (48–63)	70% (44–87)	54% (45–78)	61% (59–65)	97% (55–97)	0.41 †	≥ 40%
% Solid 4 hours, median (IQR)	94% (89–98)	93% (90–97)	96% (86–97)	95% (82–98)	86%	0.72 †	≥ 90
Small Bowel							
Abnormal, n (%)	0/4 (0%)	2/15 (13%)	4/34 (12%)	1/10 (10%)	3/3 (100%)	**0.02** *	n/a
% emptying at 6 hours, median (IQR)	79% (68–92)	66% (58–86)	76% (56–82)	68% (56–82)	28% (16–40)	**0.03** †	≥ 49%
Colon							
Abnormal, n (%)	3/4 (75%)	10/15 (67%)	18/33 (55%)	8/10 (80%)	2/3 (66%)	0.52 *	n/a
% emptying at 72 hours, median (IQR)	81% (57–91)	53% (0–85)	60%(16–88)	3.5% (0–32)	18% (0–76)	0.07 †	≥ 67%
Disease duration from 1st symptom (yrs), median (IQR)	4.0 (4–5)	10 (6–18)	12 (7–24)	20 (10–26)	12 (7–27)	0.07 †	n/a

Medsger severity scores defined as: 1, requiring GERD medications; 2, refractory reflux requiring high dose GERD meds and/or evidence of small bowel dilation on radiography; 3, pseudo-obstruction and/or malabsorption syndrome; 4, TPN required.

Abbreviations: IQR, interquartile range; %, percentage; t½: half-time, sec: seconds, min: minutes.

* Significance determined by Fisher's exact test

† Significance in trend across Medsger score determined by linear regression.

Table 4.

Spearman correlation table between whole gut transit study and GI symptoms (UCLA GIT 2.0)

	GIT Reflux	GIT Dist/ Bloat	GIT Soilage	GIT Diarrhea	GIT Social	GIT Emotional	GIT Constipation	GIT total score
ETT	0.27*	0.16	0.02	**0.37**	0.23	0.14	−0.06	0.17
E10s	−0.31*	0.00	−0.06	−0.25	−0.15	−0.04	0.08	−0.10
Stomach 1hr	−0.16	−0.09	0.01	0.00	−0.02	−0.04	0.04	−0.12
Stomach 2hr	−0.20	−0.19	0.08	−0.12	−0.09	−0.09	−0.08	−0.14
Stomach 3hr	−0.34*	−0.27†	−0.01	−0.22	−0.26†	−0.03	−0.04	**−0.30**
Stomach 4hr	−0.14	−0.12	0.09	0.03	−0.12	−0.05	0.05	−0.09
Small bowel	0.03	−0.22	0.04	−0.14	−0.23	−0.25	−0.12	−0.20
Large bowel	−0.01	−0.01	−0.20	0.25	0.08	−0.21	0.12	−0.06

UCLA Gastrointestinal Tract 2.0 patient-reported scores were compared to findings on whole gut transit studies using Spearman rank-order correlation.

Abbreviations: ETT, esophageal transit time; E10s, percentage of esophageal emptying at 10 sec; Stomach × hr, solid emptying of the stomach at × hour(s); Small bowel, percentage of small bowel emptying at 6 hours; Large bowel, percentage of colonic emptying at 72 hours.

Columns above reflect the following patient-reported symptoms: reflux, distention/bloating, soilage, diarrhea, social impact of GI symptoms, emotional impact of GI symptoms, constipation. Bolded values signify p value <0.05.

*p-value of 0.05.

†p-value of 0.06.