Associations between a scleroderma-specific gastrointestinal instrument and objective tests of upper gastrointestinal involvements in systemic sclerosis

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Received on January 15, 2013; accepted in revised form on May 30, 2013.

Clin Exp Rheumatol 2013; 31 (Suppl. 76): S57-S63.

Key words: gastrointestinal involvement, systemic sclerosis, UCLA SCTC-GIT 2.0

Competing interests: D.E. Furst has received grant/research support from and has been a consultant for AbbVie, Actelion, Amgen, BMS, Janssen, Gilead, GSK, NIH, Novartis, Pfizer, Roche/Genentech, UCB, and is a member of speakers' bureau (CME only) for AbbVie, Actelion, and UCB; D. Khanna was supported by NIH/NIAMS K24 AR063120; the other co-authors have declared no competing interests.

ABSTRACT

Background. *UCLA-SCTC-GIT 2.0 is an instrument designed to evaluate gastrointestinal (GI) symptoms in systemic sclerosis (SSc). The objective of our study was to assess the associations between the upper GI (UGI) symptom scales (reflux and distention/bloating [D/B] scales) versus objective/laboratory studies.*

Methods. *Fifty-five patients with SSc were enrolled at 2 centres. Each patient completed the GIT 2.0 and had objective and laboratory tests. Correlations were assessed using the Spearman's test. We also assessed the average scores in patients with positive vs. negative tests and compared them using the t-test and Wilcoxon test.*

Results. *The mean (SD) age was 53.6 (11.8), 90% were women and 49% had limited SSc. The mean reflux and D/B scores were 0.82 and 1.25, respectively (moderate severity). The reflux scale had moderate correlations with upper GI objective evaluations (correlation coefficient ≥0.40) and was able to differentiate between patients with endoscopy proven esophagitis and manometric abnormalities (p=0.01 for both). D/B scores were numerically higher in patients with abnormal objective tests. The GIT 2.0 reflux and D/B scales had a high sensitivity ranging from 80% to 94% but very low specificity (range; 0–20%) based on objective gold standard GI measures.*

Conclusion. *The GIT 2.0 reflux and D/B scales have a high sensitivity (range 80–94%) for UGI involvement. The GIT 2.0 instrument complements the objective tests for assessment of the UGI.*

Introduction

Systemic sclerosis (scleroderma; SSc) is a multisystem connective tissue disorder associated with inflammation, fibrosis, and a diffuse microvasculature alteration. Approximately 90% of patients with SSc develop gastrointestinal tract (GI) manifestations (1, 2) and may present in a wide array of symptoms – from dysphagia to fecal incontinence. Involvement of the gut not only adversely affects their health related quality of life (HRQOL) (3-5) but is one of the leading causes of morbidity and even mortality (6) in patients with SSc. In addition to being very common in all SSc subsets, GI involvement is frequently one of the first organ involvements of the disease.

To assess the GIT symptoms and its impact on social functional and emotional well-being, we have developed the University of California Los Angeles Scleroderma Clinical Trial Consortium Gastrointestinal Tract Instrument (UCLA SCTC-GIT) 2.0 instrument (GIT 2.0). The instrument is a 34 item questionnaire that has shown to have acceptable validity and reliability in different studies (7-13). However, none of the studies have assessed the performance of the GIT 2.0 *versus* GI-specific objective and laboratory measures. The purpose of our study was to assess the associations between the upper GI symptom scales of the instrument (reflux and distention/bloating [D/B] scales) *vs.* the objective/laboratory measures.

Patients and methods

We recruited 55 consecutive patients with SSc at two scleroderma centres (29 patients from UCLA, USA and 26 from Cochin Hospital, France). We collected the age, sex, ethnicity, height, weight, unplanned weight loss in the past 6 months, cutaneous SSc subtype as defined by LeRoy (14) and modified Rodnan skin score of each patient. The study was performed as part of clinical care at each centre. Therefore, we

assessed objective studies performed as part of local standards. For evaluation of the esophagus, UCLA regularly performs barium swallow and upper GI endoscopy in patients with moderate-to-severe reflux symptoms. At Cochin, manometry and upper GI endoscopy is performed on regular basis whereas barium swallow is not performed for assessment of the esophagus. For evaluation of gastric dysmotility, UCLA performs a gastric emptying study using Technetium-99m sulfur colloid, and less than 60% of gastric emptying at 90 minutes was considered a delayed response. This study is done as part of clinical evaluation in UCLA whereas this is not performed at Cochin. Both centres perform regular lactulose breath test to assess potential bacterial overgrowth in case of abdominal pain, distention/bloating, chronic diarrhoea, as there is evidence of high prevalence of positive test in SSc (15, 16). Therefore, our analysis includes the following objective tests: barium swallow, gastric emptying study, lactulose breath test, gastroesophageal endoscopy (EGD), esophageal manometry, high resolution computed tomography(HRCT) of the chest, and pulmonary function test (PFT). We also captured results of various GI-specific laboratory tests (serum amylase, lipase, Ca, PT, PTT, Mg, Iron, Vitamin D, vasoactive intestinal peptide, gastrin, carotene, Methylmalonic acid, transglutaminase antibody, endomysial antibody, antigliadin antibody). Patients received appropriate empiric symptomatic treatment (including H2 blockers and proton pump inhibitors) for their clinical care.

Table I. Baseline characteristics of the patients.

Variable	n=55
Age, mean (SD)	53.6 (11.8)
Female, n (%)	50 (90.9)
Ethnicity, n (%)	
White	38 (69)
African	2 (4)
Hispanic	5 (9)
Other	10 (18)
Type of SSc, n (%)	
Limited	27 (49.1)
Diffuse	24 (43.6)
Overlap	1 (1.8)
Sine	3 (5.5)
Modified Rodnan skin score, mean (SD)	9.6 (7.9)
Height (in), mean (SD)	63.5 (3.1)
Weight (lbs), mean (SD)	136.6 (27.5)
BMI, mean (SD)	23.7 (4.7)
Unplanned weight loss, n (% of total body weight)	
<5%	45 (81.8)
≥5%	10 (18.2)
Forced Vital Capacity % predicted, mean (SD)	89.1 (24.3)
Diffusion Capacity(DLCO) % predicted, mean (SD)	69.0 (22.1)
High Resolution CT (n=53)	
Normal, n (%)	23 (41.8)
Ground glass opacity, n (%)	16 (30.2)
Fibrosis, n (%)	28 (52.8)

UCLA SCTC GIT 2.0

Patients completed the GIT 2.0 during their clinic visit. GIT 2.0 is a validated, patient-reported outcome measure to assess HRQOL and GIT severity in SSc, both in English and French (9-11, 17). This 34-item instrument has seven scales: reflux, distention/bloating, diarrhoea, fecal soilage, constipation, emotional well-being, and social functioning and a total GI score. All scales are scored from 0 (better HRQOL) to 3 (worse HRQOL) except diarrhoea and constipation scales that ranges from 0–2 and 0–2.5, respectively. The total GI score is the average of 6 of 7 scales (excludes constipation) and total GI score are scored from 0 (better HRQOL) to 2.83 (worse HRQOL). Based on an online survey of scleroderma patients belonging to the National Scleroderma Foundation and data from our previous publications, the GI-related severity is divided into tertiles, which we labeled as: none to mild symptoms, moderate symptoms, and severe-to-very severe symptoms. For the reflux scale, this translates into 0.00–0.49 (none-to-mild), 0.50–1.00 (moderate), 1.01–3.00 (severe-to-very severe) and for the Distension/Bloating (D/B) scale, 0.00-1.00 (none-to-mild), 1.01–1.60 (moderate), and 1.61–3.00 (severe-to-very severe). The GIT 2.0 in English and other versions is available for free-of-charge use online at http://uclascleroderma.researchcore.org/. A French version of this questionnaire has been validated in a previous study (9).

Every effort was made to complete the objective tests within 1 week of answering the GIT 2.0. In cases where it was not possible due to scheduling or insurance issues, we readministered the GIT 2.0 and used the recent version for the analysis. We hypothesised moderate correlations (r ≥0.40) between the reflux scale scores and the barium swallow, upper GI endoscopic findings, and esophageal manometric abnormalities. We also hypothesised moderate correlations between the D/B scale scores and the lactulose breath test, gastric emptying study, unplanned weight loss, and laboratory tests. These correlations were chosen due to known associations of specific GIT disorders (*e.g.* small intestinal bacterial overgrowth [assessed by lactulose breath test] and symptoms of distention/bloating (18))

Statistical analysis

For descriptive purposes, continuous variables are described as mean (SD), while categorical variables are described as n (%). Association between GIT 2.0 and objective tests was determined in three ways: 1) assessing Spearman correlations and their associated *p*-values, 2) comparing average scores in patients with positive *versus* negative objective tests using the Wilcoxon and Student *t*-tests, as appropriate for the distribution, and 3) computing the sensitivity and specificity of the reflux and D/B scales for clas-

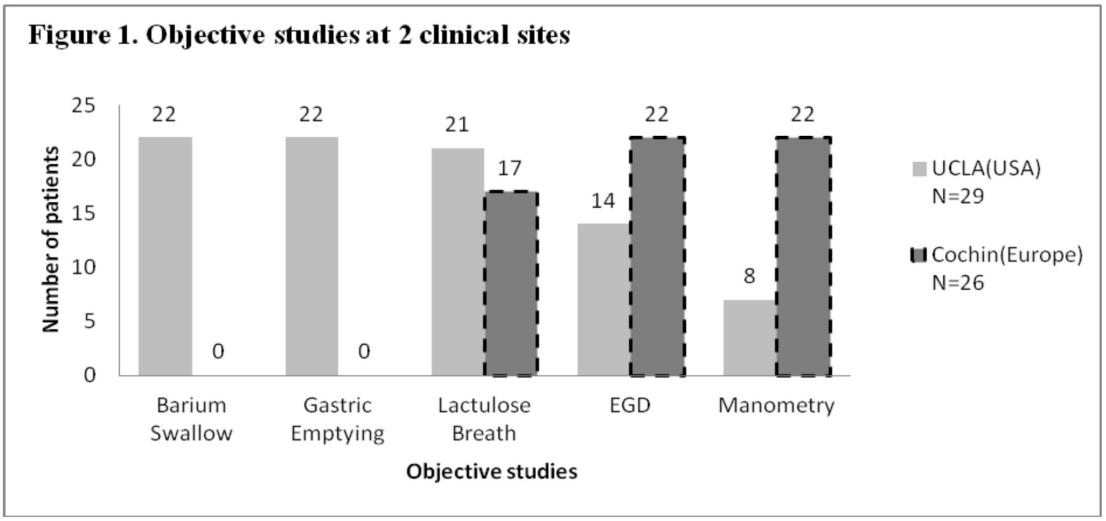

Fig. 1. Objective studies at 2 clinical sites.

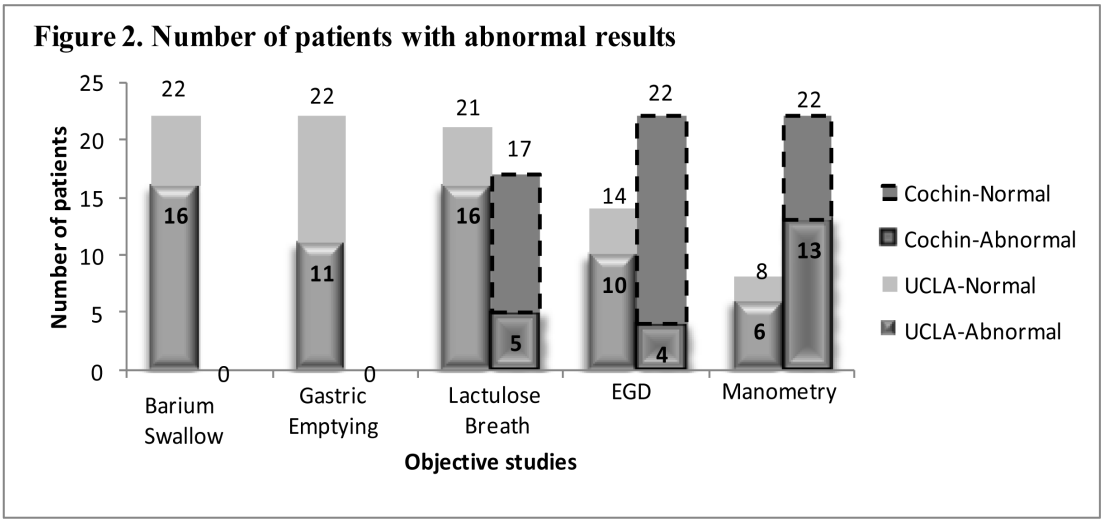

Fig. 2. Number of patients with abnormal results.

sifying positive *versus* negative objective tests. Normal *versus* abnormal on the objective tests were treated as the disease status, and the Reflux and D/B scales were treated as the diagnostic tests, where a Reflux and D/B score of 0 was defined as "No symptoms", and a 0.5–3.00 Reflux score and a 1.01–3.00 D/B score was defined as "moderate-severe" symptoms. Analysis was carried out using R version 2.14.0 (19).

Results

Baseline characteristics

The mean (SD) age was 53.6 (11.8), 91% of patients were women, and 69% were Caucasian. The mean MRSS was 9.6 units and 49% of the participants had limited SSc (Table I). Mean (SD) disease duration was 8.8 (6.3) years. The mean (SD) FVC% was 89.1 (24.3) % predicted and DLCO was 69.0 (22.1)% predicted. On HRCT, 30% of patients had ground glass opacity and 53% of patients had some degree of fibrosis while 42% of the patients were normal. All patients were on the appropriate symptomatic treatment for GI complaints including proton pump inhibitors in 50/55 (90%) and prokinetic agents in 18/55 (33%) patients as well as immunosuppressive/immunomodulatory medications for their underlying disease.

The GIT 2.0 had a mean (SD) reflux score of 0.82 (0.64; moderate) with 36 (65%) patients having significant Reflux score ≥0.5, mean D/B score of 1.25 (0.85; moderate) with 27 (49%) patients having significant D/B score >1.0. Twenty-one (38%) patients had significant scores in both and 2 (4%) patients had scores of 0 in both. Average Reflux and D/B scores were 0.94 and 1.38 for limited SSc and 0.72 and 1.12 for diffuse SSc. Mean (SD) value for other GIT 2.0 scales were as follows; 0.54 (0.73; moderate) for diarrhoea, 0.65 (0.67; moderate) for constipation, 0.40 (0.74; mild) for fecal soilage, 0.58 (0.63; moderate) for emotional well-being, 0.52 (0.54; moderate) for social functioning and 0.69 (0.47; moderate) for the total GIT score. We analysed the difference in each scale between patients with early disease *versus* late disease divided by the median value (8 years) of disease duration, which showed mean [SD] of 3.8 [2.1] years for early disease and 13.7 [4.9] years for late. There were differences in the fecal incontinence (early disease = 0.13 [0.43] *vs*. late disease 0.64 [0.87]) and total score (early disease = 0.55 [0.43] *vs*. late disease 0.81 [0.45]; $p<0.05$). No other significant differences were seen in other scales.

Table II. Correlations between GIT 2.0 and objective/laboratory studies.

UCLA SCTC GIT 2.0	Objective study	Spearman correlation	Score in patients with positive test	Score in patients with negative test	*p*-value
Reflux scale	Upper GI endoscopy (n=36)	0.46*	Esophagitis (n=14) 1.38 (0.54)	Normal (n=22) 0.76 (0.58)	0.01
	Esophageal manometry (n=30)	0.51*	Decreased peristalsis (n=19) 1.39 (0.70)	Normal (n=11) 0.69 (0.59)	0.01
		0.48*	Decreased LES pressure (n=13) 1.42 (0.65)	Normal (n=17) 0.75 (0.64)	0.01
	Barium swallow (n=22)	0.26	Dysmotility/GERD (n=16) 0.93 (0.69)	Normal (n=6) 0.77 (0.46)	0.58
	HRCT (n=53)	-0.26	Fibrosis (n=28) 0.62 (0.52)	Normal (n=23) 0.96 (0.69)	0.06
		-0.11	Ground glass (n=16) 0.62 (0.37)		0.45
	FVC (n=53)	0.1	FVC<65% (N=9) 0.84 (0.62)	FVC>65% (n=44) 0.81 (0.64)	0.83
Distention / Bloating scale	Lactulose breath test (n=38)	0.07	Bacterial overgrowth (n=21) 1.35 (0.94)	Normal (n=17) 1.12 (0.91)	0.67
	Gastric emptying study (n=22)	0.13	Delayed (n=11) 1.48 (1.15)	Normal (n=11) 1.14 (0.73)	0.55
	Unplanned wt loss (n=53)	0.16	>5% of TBW (n=10) 1.46 (0.71)	<5% of TBW (n=43) 1.12 (0.90)	0.24
	Calcium (n=25)	-0.19	Abnormal (n=2) 1.5 (0.35)	Normal (n=23) 1.34 (1)	0.65
	PT (n=43)	0.11	Abnormal (n=23) 1.22 (0.78)	Normal (n=20) 1.07 (0.96)	0.34
	PTT (n=43)	-0.16	Abnormal (n=20) 1.09 (0.79)	Normal (n=23) 1.21 (0.93)	0.95
	Serum carotene (n=21)	-0.12	Abnormal (n=5) 1.15 (1.1)	Normal (n=16) 1.42 (1.0)	0.59
	Serum gastrin (n=32)	0.02	Abnormal (n=18) 1.3 (0.89)	Normal (n=14) 1.36 (1.16)	0.95
	Vitamin D (n=45)	-0.05*	Abnormal (n=27) 1.85 (0.64)	Normal (n=18) 1.14 (0.87)	0.03
	Methylmalonic acid (n=23)	0.06*	Abnormal (n=8) 1.95 (0.96)	Normal (n=15) 1.1 (0.97)	0.05

*p<0.05; n: number of patients in each category that answered the GIT 2.0 questionnaire.

Objective studies

Patients had EGD, esophageal manometry, barium swallow, gastric emptying test, and lactulose breath test (Fig. 1-2, Table II). Of the 36 patients who had an EGD, 14 (39%) showed signs of esophagitis, 1 (3%) with gastric ulcer, and 5 (14%) with biopsy confirmed Barrett's esophagitis. On esophageal manometry 19 (63%) patients had either decreased motility or aperistalsis and 13 (43%) had a decreased lower esophageal sphincter pressure. Barium swallow with small bowel follow through revealed spontaneous gastroesophageal reflux or dysmotility in 16 (73%) patients. The gastric emptying test showed 11 (50%) patients had delayed gastric emptying. Twenty-one (55%) patients who had a lactulose breath test showed abnormal studies indicating small bowel bacterial overgrowth and 10 (19%) patients experienced unplanned weight loss of greater than 5% of their total body weight in the past 3–6 months.

The reflux scale had moderate correlations (correlation coefficients ≥0.40) with upper GI objective evaluations and was able to differentiate between patients with EGD proven esophagitis and manometric abnormalities (Table II). Patients with esophagitis on EGD had significantly higher GIT 2.0 reflux scores compared to patients with normal EGD (1.38 *vs*. 0.76; p=0.01). Similar trend in the reflux scores were also seen in esophageal manometry results (mean reflux score in patients with decreased peristalsis was 1.39 *vs*. 0.69 in patients without, reflux score was 1.42 in patients with decreased LES pressure *vs*. 0.75 in patients without; p=0.01 for both). There were no significant associations between the reflux scores and HRCT or PFT findings. Despite non-significant associations between the reflux scale and abnormal findings on the barium swallow, the patients with

Table III. Discordance between the GIT 2.0 scales and objective measures.

Objective Study		Reflux scale	
		No symptoms (reflux score: 0; n=3)	Moderate-severe symptoms (reflux score: 0.50–3.00; n=36)
Manometry	Normal (n=11)	1	8
	Abnormal (n=19)	1 (Decreased peristalsis)	16
Barium Swallow	Normal (n=6)	0	5
	Abnormal (n=16)	2 (GERD, GERD and Dysmotility)	12
EGD	Normal (n=22)	1	11
	Abnormal (n=14)	1 (Esophagitis)	10
	Barrett's (n=5)	0	1
		Distention/Bloating scale	
		No symptoms (D/B score: 0, n=5)	Moderate-severe symptoms (D/B score: 1.01–3.00, n=27)
Lactulose Breath	Normal (n=17)	2	8
	Abnormal (n=21)	2	11
Gastric Emptying	Normal (n=11)	0	5
	Abnormal (n=11)	2	8

Table IV. Sensitivity/specificity of GIT 2.0 *vs*. the objective tests (gold standard).

Objective study	Sensitivity (%)	Specificity (%)
Esophageal Manometry*	94.12	11.11
Barium Swallow study*	85.71	0.00
Upper GI endoscopy (EGD)*	90.91	8.33
Lactulose Breath Test**	84.62	20.00
Gastric Emptying Study**	80.00	0.00

**vs* Reflux scale; ***vs*. Distention/ Bloating scale.

abnormalities on the barium swallow had higher mean reflux score compared to patients with a normal barium swallow (mean (SD) reflux score of patients with dysmotility or GERD on barium swallow was 0.93 (0.69) *vs*. 0.77 (0.46) for patients with normal barium swallow, *p*=NS).

For D/B scores, although there was a trend in which D/B scores were numerically higher in patients with the abnormal findings on the hypothesised objective/laboratory tests (lactulose breath test: 1.35 *vs*. 1.12, gastric emptying study: 1.48 *vs*. 1.14, unplanned weight loss: 1.46 *vs*. 1.12; *p*=NS for all) these were non-significant associations (Table II).

Laboratory tests showed that 60% of patients had reduced vitamin D levels (defined as less than 30 ng/ml), 56% had elevated gastrin (>100 pg/ml), 52% had prolonged PT(>11.2 seconds), and 35% had elevated methyl malonic acid(MMA) (>320nmol/L; not shown in tabulated form). No patients had positive antibodies to the coeliac panel. As most would expect severity of symptoms to be correlated with abnormal objective tests, and abnormal tests to reflect the presence of symptoms, we explored the proportion of patients who had moderate-to-severe upper GI symptoms but normal objective tests and vice versa. Among patients who had moderate to severe reflux symptoms (reflux score ≥0.5) 33% (8/24) had normal peristalsis on manometry, 29% (5/17) patients had normal barium swallow and 52% (11/21) had a normal appearance on EGD (Table III). Conversely, no reflux symptoms were seen in 5% (1/19) of patients with abnormal peristalsis, 13% (2/16) of patients with abnormal barium swallow, and 7%(1/14) of patients with abnormal EGD. Other proportions are shown in Table III.

We calculated the sensitivity and specificity of the GIT 2.0 reflux and D/B scales based on each objective gold standard GI measures. The GIT 2.0 scales had a high sensitivity, ranging from 80% to 94% but very low specificity (range; 0–20%) (Table IV) when compared to the objective tests.

Discussion

Gastrointestinal involvement affects approximately 90% of SSc patients, with nearly 50% being clinically significant (6, 20). The GIT 2.0 was developed to capture gastrointestinal involvement in patients with SSc and has been found to be feasible and reliable for the assessment of patients' GI symptoms (7-9). Our data shows that GIT 2.0 reflux and D/B scales are sensitive in assessing GI involvement and complement the objective tests.

Objective studies are the gold standard of diagnosis for GI involvement in SSc. Upper GI endoscopy assesses the mucosal involvement of the esophagus and stomach, whereas barium swallow, gastric emptying and manometry assess motility. However, routine evaluation for GI involvement via objective measures in patients with SSc is generally limited due to the availability of the procedures, uniform interpretation, insurance approval, and potential procedure-related adverse events. However, there is a great need to evaluate GI symptoms in patients with SSc on a routine basis due to high prevalence in SSc population (21). A patient-reported instrument provides a simple tool to assess GI symptoms and has been used by many investigators (21-23). Due to limitations of objective tests, treatment of GI involvement is generally based on symptoms (23). Objective tests are usually performed when initial treatment is not effective or there are additional medical reasons (*e.g*. undergoing major surgery).

We utilised a validated instrument to assess the GI symptoms in consecutive patients seen at 2 large scleroderma centres. We focused on the upper GIT for our evaluation because there is a greater prevalence of upper GI involvement in SSc and the objective tests relating to the upper GI tract are easier to perform in many centres.

Our current study shows that the GIT 2.0 reflux scale has moderate correlations with the presence of esophagitis on EGD and decreased peristalsis and lower LES pressure on esophageal manometry. There were also non-significant trends between D/B scale and abnormal lactulose breath tests and gastric emptying study. Furthermore, our data suggests that reflux and D/B scales have high sensitivity (80%–94%) but poor specificity for the presence of UGI abnormalities. This suggests that absence of reflux and D/B symptoms rule out any significant abnormalities on objective evaluation of the UGI but a positive test is not able to differentiate between different mucosal/motility disorders. This may be due to variety of reasons. First, patients with small intestinal bacterial overgrowth and gastroparesis (as an example) have symptoms of D/B and thus presence of D/B is not specific for either disorder. D/B symptoms can also been seen with involvement of large bowel involvement. Second, the presence of false positives/negatives of the objective tests may lead to this disparity. For example, the reflux symptoms may be due to increased subjective sensitivity without presenting with gross lesion on UGI endoscopy, and that patients with negative findings can develop mucosal lesions during follow up exams (24). Also, the accuracy of endoscopies can depend on the observer; further, even if the mucosa appears grossly normal, this does not necessarily mean it is also histologically normal. Therefore, the absence of endoscopic findings does not exclude the diagnosis of SSc related GI disease. Similarly, the data on lactulose breath tests shows variability in sensitivity and specificity for the diagnosis of SIBO (16, 25, 26).

We evaluated multiple laboratory tests that may be associated with GI involvement (especially malabsorption), as decreased absorption of the gut may result in the lower blood concentration of nutrients. Reduced vitamin D levels and abnormal calcium metabolism have been noted in the past (27-29) and studies suggest it may be caused by decreased gut absorption(of calcium) and fibrosis of the skin (thus decreasing Vit D activation). Methylmalonic acid (MMA) is a good surrogate for cobalamin (vitamin B12) status (30) and malabsorption or malnutrition would be reflected by fluctuating MMA levels. Serum carotene levels and PT/aPTT correlated with severe intestinal malabsorption in the past (31). Elevated gastrin levels have been found and could have been a result of impaired gastric secretion and motility, but also could have been caused by proton pump inhibitors which most patients were taking (32, 33). Our study showed significantly higher D/B scores in patients that had abnormal vitamin D and MMA levels, but no significant correlation in other lab values.

Our study has limitations. The majority of the limitations are related to the clinical nature of the study as we tried to explore the utility of GIT 2.0 in clinical care. First, since this study was performed as part of clinical care, not all patients had all objective studies and many patients were receiving empiric symptomatic treatment which may also influence the results. We analysed two patient populations with different treatment protocols and missing data were inevitable. Second, GIT 2.0 questionnaires and studies were not conducted on the same day (which would have been ideal), but every effort was made to do this within 1 week of each other and it is our belief that the underlying GI disease changes very little in 1–2 weeks. Third, the evaluation of the esophagus was limited as further testing such as manometry or EGD was not routinely performed, and we did not gather data of esophageal pH monitoring. Diagnoses such asymptomatic esophageal dysmotility, asymptomatic but pathologic GERD and non erosive reflux disease might be not adequately diagnosed in this setting. Finally, patients' treatments were undertaken on a clinical basis and were varied, although specific treatment plays a negligible role in a cross-sectional analysis.

In conclusion, we present the correlation between subjective upper GI symptom severity and objective studies. We have found the GIT 2.0 reflux and D/B scales are highly sensitive for presence of abnormalities on structural/motility tests and can be used as initial screening tests in routine practice. Further study in a more systematic manner will help further define the GIT 2.0 for research purposes.

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