Effect of Gastrointestinal Manifestations on Quality of Life in 87 Consecutive Patients with Systemic Sclerosis

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ABSTRACT. ***Objective.*** To assess the effect of gastrointestinal (GI) manifestation on the quality of life in patients with systemic sclerosis (SSc).

Methods. The University of California, Los Angeles Scleroderma Clinical Trial Consortium Gastrointestinal Tract 2 questionnaire was completed by 87 consecutive patients with SSc attending the scleroderma clinic at a single center. Their clinical features and current therapies were recorded; 100 patients with rheumatologic disorders other than SSc were used as controls. Individual scores were compared between SSc and controls, and between SSc subgroups.

Results. Of 87 patients, 76 (90%) were women. Median age was 55 years and disease duration 105 months. Thirty-three (38%) had diffuse and 54 (62%) had limited SSc. Patients with SSc had a higher score than controls in all domains ($p < 0.05$). Numbers of patients who responded positively to individual questionnaire components are as follows: any GI symptom 86 (99%), reflux 77 (89%), distension 73 (84%), soilage 19 (22%), diarrhea 44 (51%), constipation 51 (59%), well-being 43 (49%), and social 43 (49%). There was no difference between the scores of patients with diffuse and limited disease subtypes. The use of calcium channel blockers did not significantly increase the constipation score ($p = 0.99$). Patients who responded positively to the reflux, distension, diarrhea, and constipation domains had lower scores in the well-being and social domains.

Conclusion. GI manifestations, especially fecal incontinence (affecting 22% of patients), have a negative influence on the quality of life of patients with SSc. There was no difference between SSc disease subtypes. (J Rheumatol First Release April 1 2012; doi:10.3899/jrheum.110826)

Key Indexing Terms:
SYSTEMIC SCLEROSIS GASTROINTESTINAL TRACT QUALITY OF LIFE

Systemic sclerosis (SSc) is an autoimmune disease characterized by progressive fibrosis of the skin and various internal organs. There are 2 distinctive subtypes of the disease, diffuse and limited, depending on the distribution and extent of skin thickening. The gastrointestinal (GI) tract is the most common internal organ involved[1] and the third most frequent manifestation in SSc, after Raynaud's phenomenon and skin involvement[2]. It has been reported that patients with the diffuse subtype have a higher frequency of GI symptoms[3] and patients with anticentromere antibody have a lower risk[3]. Upper GI symptoms occur more frequently than those arising from the lower GI tract[3]. Esophageal dysmotility is frequently associated with dysphagia, gastroesophageal reflux, and heartburn, and occurs in up to 90% of patients with SSc[4]. Symptomatic involvement of the stomach and the small intestine is less common[4,5], but large bowel involvement, most frequently the transverse and descending colon, is a frequent cause of constipation[6,7,8,9,10]. The presence of GI involvement has been shown to be associated with a worse prognosis[11,12]. The management of GI manifestations in SSc is usually symptomatic.

Tools have been developed and validated for assessing quality of life in patients with GI diseases but none has been validated for patients with SSc[13,14,15]. The scleroderma Health Assessment Questionnaire has been validated in SSc; it contains the visual analog scale for symptoms related to the GI tract but gives only an overall assessment of GI involvement and not specifically different GI manifestations[16]. The University of California, Los Angeles Scleroderma Clinical Trial Consortium Gastrointestinal Tract (UCLA SCTC GIT 2.0) questionnaire was developed and validated to assess the effect of GIT manifestations on health-related quality of life (HRQOL)[17,18,19,20].

A study was carried out to determine whether HRQOL was adversely affected by GI manifestations in patients with SSc.

MATERIALS AND METHODS

Eighty-seven consecutive patients with SSc attending the Scleroderma Clinic at Mount Sinai Hospital, Toronto, completed the UCLA GIT 2 questionnaire during their routine clinic visit. The clinical characteristics, serology, and current treatment of patients were retrieved prospectively from their charts (Table 1). The inter-incisor distance, a measure of mouth opening, was the distance between the upper and lower incisors with the mouth fully open.

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Table 1. Clinical and immunological characteristics and treatment of patients with systemic sclerosis (SSc).

Characteristics	Diffuse, n (%)	Limited, n (%)
Subtype	33 (38)	54 (62)
Female	30 (91)	51 (94)
Median age, yrs	54	54
Median disease duration, mo	117	146
Median MRSS	16	6
Median inter-incisor distance, mm	32	37.2
Serology		
ANA (+)	31 (94)	51 (94)
Nucleolar staining pattern	2 (6)	5 (1)
Antitopoisomerase-1 (+)	9 (27)	6 (11)
ACA (+)	6 (18)	16 (30)
Organ involvement		
Renal	5 (15)	0
Lung	8 (24)	12 (22)
Cardiac	2 (6)	1 (2)
Medications		
Proton pump inhibitors	20 (61)	39 (72)
H_2 blockers	1 (3)	1 (2)
GI motility-enhancing agents	8 (24)	18 (33)
Calcium channel inhibitors	7 (21)	19 (35)
NSAID	6 (18)	12 (22)
Prednisone	5 (15)	6 (11)
Bisphosphonate	3 (9)	6 (11)
DMARD	12 (36)	17 (31)

MRSS: Modified Rodnan Scleroderma Skin score; ANA: antinuclear antibody; ACA: anticentromere antibody; GI: gastrointestinal; NSAID: nonsteroidal antiinflammatory drugs; DMARD: disease-modifying antirheumatic drugs.

Organ involvement was defined as having at least mild involvement by the Medsger disease severity scale[21].

Inclusion criteria. Patients with SSc fulfilling the American College of Rheumatology classification criteria[22] who were aged 18 years or older and were followed for at least 3 months were included for study.

Exclusion criteria. Patients with GI manifestations of other etiology including malignancy, bowel resection (unrelated to SSc complications), neuromuscular conditions (strokes, demyelinating disorders), trauma, and pregnancy were excluded.

The UCLA GIT 2 questionnaire consists of 7 scales, as follows: Reflux: Questions 1–8; Distension/bloating: Questions 9–12; Fecal soilage: Question 13; Diarrhea: Questions 14, 15; Social functioning: Questions 16–21; Emotional well-being: Questions 22–30; and Constipation: Questions 31–34. The items are scored on a 0 to 3 possible range, where 0 indicates better health and 3 indicates worse health except for questions 15 and 31, which were scored as 0 (better health) or 1 (worse health). Scale scores represent the average of items in the scale.

In addition to the 7 scale scores as above, scores from 6 of 7 scales (excluding the constipation scale) can be combined to form a total GIT score. Total GIT score sums up the overall burden (severity) of the SSc-associated GIT. The minimal important difference for each domain was recently calculated in a cohort of 115 patients[23]. The total GIT score and every individual scale score were compared between the 2 SSc disease subtypes and 100 control patients with rheumatologic disorders other than SSc. The social and well-being domains were compared in patients with and without reflux, distension, fecal soilage, diarrhea, and constipation, respectively. The controls consisted of patients with rheumatoid arthritis, n = 31 (31%), systemic lupus erythematosus, n = 19 (19%), psoriatic arthritis, n = 10 (10%), ankylosing spondylitis, n = 5 (5%), osteoarthritis, n = 4 (4%), fibromyalgia, n = 3 (3%), morphea, n = 5 (5%), and others, n = 23 (23%).

Statistical analysis. Descriptive statistics were used to summarize the data. The Wilcoxon signed-rank test was used to test the median difference in scores between patients with SSc and controls and between the 2 SSc subsets. Fisher's exact test was used when comparing the soilage values. A p value < 0.05 was considered significant.

RESULTS

Eighty-seven patients with SSc, of which 78 (90%) were women with a median age of 54 years, completed the questionnaire. The patient characteristics (disease duration and subtype, serology, other organ involvement, treatment of GI symptoms, and Modified Rodnan Skin score) are shown in Table 1. In the control group of 100 patients, 78 (78%) were women, with a median age of 54 years.

The numbers of patients with SSc who responded positively to the individual questionnaire components were as follows: any GI symptom 86 (99%), reflux 77 (89%), distension 73 (84%), soilage 19 (22%), diarrhea 44 (51%), constipation 51 (59%), well-being 43 (49%), and social 43 (49%). The rate (percentage) of positive answers to each domain of the UCLA GIT 2 questionnaire is shown in Table 2.

The statistical comparisons between the patients with SSc and controls and between SSc subtypes are shown in Table 3. Patients with SSc had statistically significantly higher component scores than controls in all domains as well as in the total score ($p < 0.05$). There was no difference in the scores between patients with diffuse and those with limited SSc (Table 3). The use of calcium channel blockers did not affect the constipation score ($p = 0.99$). The rate of fecal soilage in patients with SSc was 22% compared to 9% in the control group. Patients who responded positively to the reflux, distension, diarrhea, and constipation domains had lower scores in the well-being and social domains (Table 4).

DISCUSSION

GI involvement in SSc is very common[24]. It appears early in the disease course and has been shown to be associated with a worse prognosis[11,25]. Studies evaluating the effect of GI symptoms are scarce[26]. Our study evaluated the severity of GIT symptoms in 87 consecutive patients with SSc by a simplified questionnaire that identifies both upper and lower GI manifestations. Our results indicate a significant decrease in quality of life in patients with SSc due to GI involvement compared to control patients with other rheumatologic disorders. Recent reports from other studies using different types of questionnaires reveal similar results[1,27,28]. Franck-Larsson, *et al*[1] used a questionnaire that assessed the lower GIT with the Medical Outcomes Study Short-Form Health Survey. The rate of incontinence in their patients was 9% and 33% for solid and liquid stools, respectively[1]. Thoua, *et al* assessed patients using the first version of the UCLA GIT and found no difference between SSc subtypes or autoantibody profiles[27]. Nietert, *et al*[28] found that 26.4% of 72 patients who complet-

Table 2. The rate (percentage) of positive answers to each domain of the UCLA GIT 2 questionnaire[18].

Question	Score 0 (no days)	Score 1 (1–2 days)	Score 2 (3–4 days)	Score 3 (5–7 days)
In the past 1 week: how often did you:				
1. Have difficulty swallowing solid foods?	48 (54)	17 (20)	5 (6)	17 (20)
2. Have an unpleasant stinging sensation in your chest (heartburn)?	40 (46)	27 (31)	13 (15)	7 (8)
3. Have a sensation of bitter or sour fluid coming up from your stomach into your mouth (acid reflux)?	39 (45)	31 (36)	7 (8)	10 (11)
4. Have heartburn on eating acidic foods such as tomatoes and oranges?	52 (60)	22 (25)	7 (8)	6 (7)
5. Have regurgitate (throw up or bring up small amounts of previously eaten food)?	60 (68)	17 (20)	4 (5)	6 (7)
6. Sleep in a raised or an L-shaped position?	38 (44)	13 (15)	5 (6)	31 (35)
7. Feel like vomiting or throwing up?	57 (66)	17 (20)	3 (3)	10 (11)
8. Vomit or throw up?	72 (83)	6 (7)	2 (2)	7 (8)
9. Feel bloated (a feeling of gas or air in the stomach)?	29 (33)	22 (25)	12 (14)	24 (28)
10. Notice an increase in your belly, sometimes requiring you to open your belt, pants or shirt?	43 (49)	16 (19)	9 (10)	19 (22)
11. Feel full after eating a small meal?	34 (39)	20 (23)	10 (11)	23 (27)
12. Pass excessive gas or flatulence?	41 (47)	19 (22)	7 (8)	20 (23)
13. Did accidentally soil (dirty) your underwear before being able to get to a bathroom?	65 (78)	13 (15)	4 (5)	2 (2)
14. Have loose stools (diarrhea)?	47 (54)	21 (24)	15 (17)	4 (5)
15. In the past 1 week have you noticed your stools becoming watery?	Yes 59 (68)	No 28 (32)	—	—
In the past 1 week how often did the following interfere with social activities (such as visiting friends or relatives)?				
16. Nausea	70 (80)	10 (11)	5 (6)	3 (3)
17. Vomiting	76 (88)	4 (5)	4 (5)	2 (2)
18. Stomach ache or pain	61 (70)	12 (14)	8 (9)	6 (7)
19. Diarrhea	67 (77)	13 (15)	5 (6)	2 (2)
20. Worry about accidentally soil your underwear	69 (79)	11 (12)	6 (7)	2 (2)
21. Bloated sensation	51 (59)	15 (17)	7 (8)	14 (16)
In the past 1 week how often did you:				
22. Feel worried or anxious about your bowel problems?	51 (59)	14 (16)	11 (12.5)	11 (12.5)
23. Feel embarrassed because of your bowel problems?	63 (72)	11 (13)	6 (7)	7 (8)
24. Have problems with sexual relations because of your bowel symptoms?	83 (95)	0	1 (1)	3 (4)
25. Fear not finding a bathroom?	63 (72)	14 (16)	4 (5)	6 (7)
26. Feel depressed or discouraged due to your bowel symptoms?	66 (76)	8 (9)	5 (6)	8 (9)
27. Avoid or delay travelling because of your bowel symptoms?	71 (82)	8 (9)	5 (6)	3 (3)
28. Feel angry or frustrated as a result of your bowel symptoms?	66 (76)	5 (6)	7 (8)	9 (10)
29. Have a problem with your sleep as a result of your bowel symptoms?	66 (76)	9 (10)	5 (6)	7 (8)
30. Feel stress or an upset mood worsens your bowel symptoms?	67 (77)	8 (9)	6 (7)	6 (7)
In the past 1 week have you noticed your stools becoming:				
31 Harder?	Yes 66 (76)	No 21 (24)	—	—
In the past 1 week how often:				
32. Were you constipated or unable to empty your bowels?	53 (61)	19 (22)	12 (14)	3 (3)
33. Did you have hard stools?	53 (61)	22 (25)	10 (12)	2 (2)
34. Did you have pain while passing your stools?	60 (69)	18 (21)	5 (6)	4 (4)

UCLA GIT: University of California, Los Angeles Scleroderma Clinical Trial Consortium Gastrointestinal Tract.

ed the study had significant depressive symptoms, and of those, only 19.2% were receiving antidepressant medications. Although other SSc manifestations such as Raynaud's phenomenon, pulmonary hypertension, and fibromyalgia can independently alter the HRQOL, items used in this questionnaire specifically assess how GIT manifestations affect the HRQOL.

Symptoms of gastroesophageal reflux disease (GERD) were frequently encountered in our patients, occurring in 89% of the cohort. Proton pump inhibitors, occasionally combined with H_2 blockers, are the most effective treatment of GERD and were used in 60% to 70% of our patients. Often much higher doses are required in patients with SSc than in the treatment of GERD of other etiology. Chronic GERD, particularly if severe or undertreated, may lead to erosive esophagitis (which may bleed and result in anemia), Barrett's esophagus (with premalignant transformation of the mucosa), and stricture formation with severe dysphagia requiring esophageal dilatation.

Eighty-four percent of our patients had gastric and/or intestinal dysmotility evidenced by a positive response to the distension domain questions. Gastric stasis results in delayed emptying of the stomach, early satiety, decreased oral intake, and progressive malnutrition. Eating small but frequent meals

Table 3. Numbers (%) of patients with systemic sclerosis (SSc) with gastrointestinal (GI) symptoms and comparison with controls and between SSc subtypes.

Category	No. (%) SSc Patients with GI Symptoms	Median Scores (IQR)	No. (%) Controls with GI Symptoms	p, SSc vs Controls	p, Diffuse vs Limited Disease
Reflux	77 (89)	0.63 (0.25, 1)	52 (51)	< 0.05	0.93
Distension	73 (84)	1 (0.38, 1.75)	64 (63)	< 0.05	0.76
Soilage	19 (22)	0 (0, 0)	9 (9)	< 0.05	0.18
Diarrhea	44 (51)	0.5 (0, 1)	27 (27)	< 0.05	0.76
Constipation	51 (59)	0.25 (0, 0.75)	47 (47)	< 0.05	0.32
Well-being	43 (49)	0.11 (0, 0.67)	24 (24)	< 0.05	0.75
Social	43 (49)	0 (0, 0.67)	26 (26)	< 0.05	0.093
Any GI symptoms	86 (99)	NA	89 (88)	NA	
Total	NA	2.6 (1.1, 6.04)	NA	< 0.05	0.93

IQR: interquartile range; NA: not applicable.

Table 4. Comparison of quality of life measures between SSc patients with and those without symptoms of individual domains.

Category	Well-being	Social
With incontinence, median (IQR)	0.83 (0.5, 1.08)	1.33 (0.22, 1.78)
Without incontinence, median (IQR)	0 (0, 0.33)	0 (0, 0.36)
p	< 0.05	< 0.05
With distension, median (IQR)	0.22 (0, 0.81)	0.17 (0, 83)
Without distension, median (IQR)	0	0
p	< 0.05	0.05
With constipation, median (IQR)	0.33 (0, 1)	0.5 (0, 1)
Without constipation, median (IQR)	0	0 (0, 0.17)
p	< 0.05	< 0.05
With diarrhea, median (IQR)	0.44 (0, 1.03)	0.5 (0, 1)
Without diarrhea, median (IQR)	0 (0, 0.11)	0 (0, 0.17)
p	< 0.05	< 0.05
With reflux, median (IQR)	0.11 (0, 0.78)	0.17 (0, 0.83)
Without reflux, median (IQR)	0 (0, 0.083)	0
p	0.08	< 0.05

IQR: interquartile range.

becomes a necessity. Despite the absence of controlled studies to demonstrate efficacy in patients with SSc, prokinetic agents such as domperidone and metoclopramide are frequently used[29]. In our cohort, 30% were taking either metoclopramide or domperidone but their efficacy appears quite limited, especially in advanced disease. Percutaneous endoscopic gastrostomy can improve weight and quality of life in selected patients[30].

While constipation is the most frequent complication of colonic involvement in SSc, diarrhea with abdominal pain and bloating occurred in 50% of our patients, and usually indicates the presence of bacterial overgrowth in the small bowel. Fortunately, the problem usually responds promptly to a course of a broad-spectrum antibiotic. Recurrent intestinal pseudoobstruction is a very distressing problem for the patient and is invariably difficult to manage medically. When at an endstage, the choices of treatment include erythromycin[31], octreotide[31,32], a defunctioning ileostomy, colectomy[33,34], and total parenteral nutrition[35].

Fecal incontinence with soilage has been a frequently overlooked symptom in SSc. In our clinic we have observed it with increasing frequency. In our study fecal incontinence occurred in 22% of the patients with SSc, which is lower than the previously reported prevalence of 38%[36]. From the patient's perspective, it is one of the most distressing GI manifestations in SSc because of the inconvenience and embarrassment that it causes. Not surprisingly, fecal soilage was found to be associated with a high burden on HRQOL in these patients compared to SSc patients without incontinence. Further, fecal incontinence is a problem that is extremely difficult to deal with, both medically and surgically. Collagen deposition, fibrosis, and loss of internal anal sphincter tone are usually implicated[37]. For these patients, sphincter muscle training is usually recommended, but from personal observations is usually ineffective. Sacral nerve stimulation has been recommended and if effective, as suggested by pilot studies, would be more acceptable[38] than a defunctioning stoma or attempts at surgical repair of the sphincter. Despite the lack of randomized controlled trials, as with most manifestations in SSc, fecal soilage is based on tissue damage and not surprisingly relief is frequently ineffective or incomplete.

A recent report from the European League Against Rheumatism Scleroderma Trials and Research group made recommendations on therapies for the treatment of SSc-associated GIT manifestations[39].

One of the limitations of our study is that the 87 patients selected were consecutive (as a convenience sampling), which makes it difficult to generalize the results on the entire cohort.

Gastrointestinal manifestations place a high burden on the HRQOL of patients with SSc. Use of the UCLA GIT 2 questionnaire will help physicians to identify patients with severe GI involvement and to treat appropriately to improve their HRQOL.

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