Assessment of gastrointestinal symptoms in patients with systemic sclerosis in a UK tertiary referral centre

Nora M. Thoua¹, Catey Bunce², Geraldine Brough³, Alastair Forbes¹, Anton V. Emmanuel¹ and Christopher P. Denton³

Abstract

Objectives. The gastrointestinal tract (GIT) is affected in up to 90% of patients with SSC to a variable extent and severity. We aimed to establish the frequency and range of gastrointestinal (GI) symptoms in SSC patients at the Royal Free Hospital, a tertiary referral centre.

Methods. A 52-item, previously validated, questionnaire capturing SSC-related gut dysfunction was given to consecutive patients with SSC attending the rheumatology outpatient department. The questionnaire assesses the ‘frequency’ of five categories of symptoms and their ‘impact’ on social functioning and emotional well-being. Patients’ notes were reviewed to establish disease subtype, autoantibody profile and other internal organ involvement.

Results. We collected 402 completed questionnaires (357 females; mean age 55). Sixty-nine per cent of patients had lcSSc and 30% dcSSc with mean disease duration of 11 years. Mean questionnaire scores showed that patients have a wide range of GI symptoms. Ninety-four per cent of patients reported upper and 79% lower GI symptoms, 3% of patients reported no symptoms and 10% reported daily symptoms. There was no association between disease subtype or autoantibody profile and GI symptoms. There was a positive correlation between diarrhoea scores (high scores = best health) and pulmonary fibrosis ($r = 0.134$, $P = 0.0068$). No other association between GI symptoms and other internal organ involvement was found.

Conclusions. GI symptoms, both upper and lower, are common in patients with SSC. Patients should be asked specifically about GI symptoms as they may be under-reported and therefore under-treated. GI focused questionnaire is an effective way to assess gut symptoms and adjust treatment.

Key words: Systemic sclerosis, Gastrointestinal tract, Questionnaire, Quality of life.

Introduction

SSC is a multisystem connective tissue disorder of unknown aetiology. The gastrointestinal tract (GIT) is affected in ~90% of patients [1, 2] and gut involvement is the leading cause of morbidity and the third most common cause of mortality in patients with SSC [3]. Any part of the GIT can be affected leading to a wide range of symptoms from gastro-oesophageal reflux to faecal incontinence [4–7]. In clinical practice though, assessment of skin involvement, cardiorespiratory and renal involvement remain the focus of clinical assessment. Furthermore, extensive research has led to significant advances in the treatment of SSC-related cardio-respiratory [8, 9] and renal involvement [10, 11], as these are the commonest causes of mortality. In contrast, treatment for GIT involvement remains largely restricted to symptom control and is often inadequate resulting in a significant effect on health-related quality of life (HRQOL) [12]. HRQOL instruments are often used to assess disease activity and symptom burden in chronic rheumatological disorders such as RA [13] and SSC [14, 15], and also GIT-related disorders such as IBD [16, 17].
HRQOL instruments can be generic illness instruments measuring general health status or disease specific providing a more detailed assessment of the specific illness and its impact. Recently, Khanna et al. [18] in the USA developed a disease-specific HRQOL instrument for patients with SSc to assess their GIT-related activity and severity, which can be used in clinical trials and day-to-day care. The SSc–GIT 1.0 is a 52-item questionnaire that has seven scales: five aspects of gastrointestinal (GI) dysfunction encountered in SSc patients (namely, reflux, distension, diarrhoea, constipation and pain) and two generic aspects (emotional well-being and social functioning). The instrument has been shown to have satisfactory reliability (Cronbach’s α 0.69–0.93 for the different scales, test–retest correlation coefficient ≥ 0.69; [18]). The aim of this study was to validate this questionnaire in a UK population of patients with SSc and to assess GIT-related disease activity in patients attending the scleroderma outpatient clinic at Royal Free Hospital, a tertiary referral centre.

Methods

The SSc–GIT 1.0 questionnaire was used with permission from Dr Khanna. This questionnaire assesses the frequency of five categories of symptoms: reflux, distension, diarrhoea, constipation, abdominal pain, and the effect of symptoms on social functioning and emotional well-being.

The questionnaire assesses the number of days (divided in four scales: 0 days, 1–2 days, 3–4 days and 5–7 days) during the previous week, thus assessing frequency rather than severity of symptoms. In view of the wide range of symptoms and the nature of the disease, this is more relevant and preferable in assessing disease burden. Patients were advised to answer the questions and report on their symptoms while on their current medications, including those for GI symptoms.

Approximately 1200 SSc patients are under regular follow-up, usually seen every 6–12 months, at the Royal Free Hospital and we aimed to collect 400 completed questionnaires, as a representative sample of this patient cohort. Patients were approached while attending for their outpatient appointment from December 2007 to June 2008. All patients attending the outpatient clinic were approached and encouraged to answer the questionnaire irrespective of whether they had a history of GI symptoms. Any questionnaires with <50% of questions answered for any of the categories were excluded. The questionnaires were scored as indicated in the original paper [18]. In brief, each item was rescaled to a range of 0–100, where 100 indicates better health. Scoring for the 4-item questions (comprising all bar two questions) as follows: 1 = 100, 2 = 66.6, 3 = 33.3 and 4 = 0. The two 2-item questions were scored as follows: 1 = 0, 2 = 100. For each category, the average score was calculated. The use of a total score has not been validated and therefore this was not calculated. For each patient with a completed questionnaire, the notes were reviewed to establish disease subtype, disease duration, presence of autoantibodies and evidence of lung, heart or kidney involvement.

Any clinical record of GI involvement, symptoms or positive tests, was also recorded. All patients gave informed consent. The study was approved by the University College Hospital Research Ethics committee.

Summary statistics were computed for each GIT scale. Since data were non-normally distributed, we present medians and ranges; however, to enable comparison with previous work in this area, we also provide means and standard deviations. The proportion of patients scoring the maximum possible value for each scale (ceiling effect) and the lowest possible value for each scale (floor effect) was computed. Matrices of pair-wise correlation coefficients were computed to assess the associations between GI symptoms and to examine the associations between GI symptoms and: (i) presence of other internal organ involvement; (ii) presence of autoantibodies; and (iii) previously documented GI disease and reported symptoms. No adjustment was made for multiple testing since the analysis was exploratory. We investigated associations in all patients and then in patient subgroups although acknowledge limited power. All statistical analyses were conducted using Stata 10 Intercooled (StataCorp LP, College Station, TX, USA) statistical software.

Results

Questionnaires were collected and 402 completed questionnaires were analysed. All the patients’ notes were reviewed and demographics, disease characteristics and other internal organ involvement were recorded. The patients’ demographics and disease characteristics are shown in Table 1. Thirty-nine per cent of patients were

<table>
<thead>
<tr>
<th>Table 1 Patient demographics and disease characteristics</th>
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<tr>
<td><strong>Characteristics</strong></td>
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<tr>
<td>Age, mean (s.d.), years</td>
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<td>Sex, F/M, %</td>
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<td>Disease duration, median (range), years</td>
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<td>Disease subtype—lcSSc/dcSSc, n (%)</td>
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<td>Internal organ involvement, n (%)</td>
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<tr>
<td>Cardiac</td>
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<td>Renal</td>
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<td>GI</td>
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<td>Autoantibodies, n (%)</td>
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<tr>
<td>ANA</td>
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<tr>
<td>ACA</td>
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<td>SCL-70</td>
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<td>U3-RNP</td>
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<td>RNAP</td>
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<td>U1-RNP</td>
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<td>Other</td>
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SCL-70: anti-topoisomerase antibody; RNAP: anti-RNA polymerase.
on immunosuppressants (mycophenolate 16%, MTX 12%, AZA 8%) and 72% were on medications for GI symptoms. The majority of patients was female (88.8%) with a mean age of 55 years and median disease duration of 10 years (range 1–52 years). Sixty-nine per cent of the patients who completed the questionnaire had lcSSc and 30% dcSSc. There were two patients with autoimmune RP and one patient with scleroderma sine scleroderma. Patients with overlap syndromes were categorized according to the SSc disease subtype. The disease subtype and autoantibody profile reflected the overall Royal Free Hospital patient cohort [19].

The SSc–GIT 1.0 questionnaires were scored as described above. The findings are summarized in Table 2.

<table>
<thead>
<tr>
<th>SSc–GIT 1.0 scales</th>
<th>Sample size</th>
<th>No. of items</th>
<th>Median score (IQR)</th>
<th>Mean (s.d.)</th>
<th>Min score</th>
<th>Max score</th>
<th>Floor effect, %</th>
<th>Ceiling effect, %</th>
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</thead>
<tbody>
<tr>
<td>Reflux</td>
<td>402</td>
<td>9</td>
<td>81.5 (59.3–92.6)</td>
<td>73.99 (23.92)</td>
<td>7.4</td>
<td>100</td>
<td>0</td>
<td>14.9</td>
</tr>
<tr>
<td>Distension</td>
<td>402</td>
<td>6</td>
<td>72.2 (50–88.9)</td>
<td>69.16 (23.84)</td>
<td>5.6</td>
<td>100</td>
<td>0</td>
<td>13.2</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>402</td>
<td>3</td>
<td>88.9 (44.4–100)</td>
<td>75.17 (30.39)</td>
<td>0</td>
<td>100</td>
<td>1.5</td>
<td>49.8</td>
</tr>
<tr>
<td>Constipation</td>
<td>401</td>
<td>3</td>
<td>100 (55.5–100)</td>
<td>76.63 (29.95)</td>
<td>0</td>
<td>100</td>
<td>2.7</td>
<td>53.2</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>401</td>
<td>2</td>
<td>100 (66.7–100)</td>
<td>80.59 (26.68)</td>
<td>0</td>
<td>100</td>
<td>3.5</td>
<td>51</td>
</tr>
<tr>
<td>Social functioning</td>
<td>401</td>
<td>20</td>
<td>96.7 (85–100)</td>
<td>89.73 (15.69)</td>
<td>12</td>
<td>100</td>
<td>0</td>
<td>42.3</td>
</tr>
<tr>
<td>Emotional well-being</td>
<td>401</td>
<td>9</td>
<td>88.9 (57.4–100)</td>
<td>76.19 (30.64)</td>
<td>0</td>
<td>100</td>
<td>1</td>
<td>43.8</td>
</tr>
</tbody>
</table>

IQR: interquartile range.

The SS–GIT 1.0 questionnaires were scored as described above. The findings are summarized in Table 2. Overall, there was a high prevalence of GI symptoms. Seventy-two per cent of patients were taking medication for GI symptoms, predominantly acid suppressants (71%), prokinetics (13%) and laxatives (4%). Despite this, 94% reported upper and 79% lower GI symptoms. In fact, the patients on acid suppressants or prokinetics (AS/P) reported more frequent reflux and distension symptoms than the patients who were not on acid suppressant or prokinetics [reflux: AS/P: 70.36 (1.467) vs no AS/P: 83.49 (1.665); distension: AS/P: 66.39 (1.437) vs no AS/P: 76.42 (1.931); P < 0.001]. With regard to frequency of symptoms, 97% of patients reported symptoms at least weekly, and 15% reported daily symptoms; only 3% of patients reported no symptoms. Figure 1 depicts the percentage of patients reporting symptoms for each frequency category.

The mean scores (s.d.) (possible score 0–100) ranged from 69.16 (23.84) for distension to 89.73 (15.69) for social functioning (Table 2). We found that distension and reflux were the categories with the lowest scores, meaning that patients complain of these symptoms most frequently. All seven scales showed a ceiling effect [percentage of patients who reported no symptoms for that scale thus scoring 100 (highest score) for the scale]. This ranged from 13.2 and 14.9% for reflex and distension scales, respectively to 53.2% for the constipation scale. The lower ceiling effect on the reflux and distension scales reflects not only the higher prevalence of these symptoms but also the fact that there were more questions in these domains than in the diarrhoea and constipation domains. Only three of the seven scales showed a floor effect [percentage of patients having the lowest score (0) for a category] and this was small, ranging from 1.5% for diarrhoea to 3.5% for abdominal pain.
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The effect on emotional well-being was most marked, with an average score of 76.2. We found strong evidence of associations between emotional well-being and all other symptom category scores. The strongest correlation was with reflux ($r = 0.47$), whereas the weakest one was constipation ($r = 0.18$). There was also significant correlation between all symptom categories and the effect on social life ($r = 0.23–0.63$).

We found little evidence of any difference in symptom scores in any of the categories between the two disease subtypes. With regard to autoantibody profile, U3RNP antibodies were associated with more frequent diarrhoea symptoms ($P = 0.015$). There was a trend towards less frequent reflux symptoms in patients with PM-Scl antibodies, but this was not statistically significant. There was no significant association with U1RNP and GI symptoms or any other significant association between autoantibody profile and GI symptoms.

We looked for an association between GI symptoms and the presence of other internal organ involvement. We found an association between diarrhoea scores and pulmonary fibrosis ($r = 0.1347$, $P = 0.0068$), that is patients with pulmonary fibrosis were less likely to have diarrhoea. In contrast, there was a negative correlation between constipation scores and pulmonary fibrosis, although this did not reach statistical significance ($r = 0.096$, $P = 0.0547$). Specifically, we did not find significant association between cardiac disease and GI symptoms, although case reports have suggested that diarrhoea and malabsorption can exacerbate cardiac complications, most likely secondary to electrolyte imbalances. Investigating whether more frequent GI symptoms were associated with other internal organ involvement, the groups were split into two groups according to scores, with those $<66.6$ depicting more frequent symptoms, as this would be equivalent according to the questionnaire to symptoms $>1–2$ days/week as an average for the category, suggestive of more severe GI involvement. No associations were found between either of the two severity groups and evidence of other internal organ involvement. Interestingly, although it has been previously suggested that severe gastro-esophageal reflux may contribute to pulmonary fibrosis [20, 21], such an association was not evident from our data. We did find though that patients with pulmonary fibrosis were more frequently taking acid suppressants than patients without pulmonary fibrosis (78% vs 66%; $P = 0.01$).

In order to assess whether the questionnaire scores correlated with previously documented GI disease and reported symptoms, patients’ notes were reviewed and any GI diagnosis or report of symptoms noted as reflux, gastroparesis, bacterial overgrowth, diarrhoea, constipation and anorectal symptoms (prolapse or faecal incontinence). Comparing the respective questionnaire scores (reflux, distension, diarrhoea and constipation), there were significantly higher scores for all the questionnaire categories (reflux: $P < 0.0001$, distension $P < 0.0001$, diarrhoea $P < 0.0001$ and constipation $P = 0.05$) in patients with GIs, compared with those without, gut involvement.

There was no available documentation on the severity of GI involvement and therefore we could not correlate this with questionnaire scores. Unfortunately, GI investigation results were often not available as tests were frequently done at patients’ local hospitals. We could not therefore correlate symptoms with objective measures.

Discussion

The development of SSc–GIT 1.0 by Khanna et al. [18] provided the first HRQOL instrument to capture GI involvement in patients with SSc. We have confirmed a similar burden of disease in a UK cohort to that reported in the US population in which the questionnaire was developed. The high frequency of GI involvement in SSc is well documented and it has a major impact on the quality of life (QOL). A number of studies have demonstrated GI involvement of both the upper and lower GI tract based on endoscopic findings or physiological studies as well as reported symptoms [7, 22, 23]. This questionnaire is designed to provide information not only about symptoms but also about the psychological impact and the effect on the patient’s social life. The questionnaire analysis showed that patients often reported both upper and lower GI symptoms, although upper GI symptoms such as reflux symptoms and dysphagia occur more frequently.

There is a significant effect of gut symptoms on emotional and social well-being.

The SSc–GIT 1.0 has seven scales: reflux, distension, diarrhoea, constipation, pain, emotional well-being and social functioning. Khanna et al. [18] had joined the reflux and indigestion scales into one bigger category as they found a strong correlation between the two categories [18]. We chose to keep them separate in our analysis as it is known that the distension scale is indicative of gastrointestinal and small bowel involvement. We did find though a high correlation between them as reported previously. All seven scales showed some ceiling effect, ranging from 13–15% in reflux and indigestion to 50–53% in diarrhoea, constipation and abdominal pain. The higher ceiling effect in the latter three symptoms may reflect a lower prevalence of lower GI symptoms. Another reason may be that fewer items were dedicated to those symptoms (three for diarrhoea, three for constipation and two for pain). Khanna et al. [18] found a much lower ceiling effect in the reflux/indigestion scale. The higher ceiling effect in our study may be explained by the larger number of patients. Overall, the mean questionnaire scores that we documented were comparable although a bit higher than those published by Khanna et al. [18]. Higher scores reflect lower symptom burden and this may well be a reflection of the larger sample size, including patients with no GI symptoms. Additionally, a large percentage of patients were on regular medication for their GI symptoms.

General GI involvement has not been associated previously with a specific disease subtype [24], unlike other internal organ pathology such as pulmonary hypertension or renal crisis, which are associated with lcSSc and dcSSc, respectively. Nishimagi et al. [25] investigated 302 patients with SS and found that in patients with
early severe GI involvement, defined as malabsorption, pseudo-obstruction or need for hyper-alimentation, the ratio of dcSSc to lcSSc was higher than in patients without severe GI involvement. They also found that these patients were less likely to suffer from interstitial lung disease. In that study, the presence of ACA or SCL-70 antibodies was less frequent in patients with severe GI involvement and there was a higher frequency of anti-U3RNP and anti-U1RNP and other ANAs [25]. However, Steen, investigating features associated with specific autoantibodies found that subjective GI involvement occurred in >80% of patients without association with specific disease subtype or autoantibodies, but severe GI involvement was significantly greater in patients with anti-U3RNP and also Th/To and anti-U1RNP [26]. Our findings are consistent with these latter results as we found no association with disease subtype or autoantibodies with general subjective GI involvement. We did find though a higher incidence of more severe diarrhoea symptoms in patients with anti-U3RNP antibodies, but not so with anti-U1RNP. The frequency of other autoantibodies such as anti-KU and anti-Th/To was too small for any meaningful associations.

We also found an inverse relationship between symptoms of diarrhoea and pulmonary fibrosis. Diarrhoea is often secondary to small intestinal involvement and bacterial overgrowth, and it is therefore probably the best symptom category indicative of severe GI involvement. It may be that treatment for pulmonary fibrosis has some protective effects against intestinal involvement although review of patients’ medications did not reveal any association between specific medications or immunosuppression and GI symptoms. Patients with pulmonary fibrosis were as expected more frequently on immunosuppressants but interestingly there was no difference in the frequency of diarrhoea symptoms with immunosuppressant use. Previous studies have suggested that severe reflux may contribute to the development of pulmonary fibrosis [20]. We did not find evidence of more severe reflux symptoms in patients with pulmonary fibrosis. An explanation for this may be that reflux symptoms often do not represent severity of oesophageal disease, for example patients with Barrett’s oesophagus often have less severe symptoms [27]. Another explanation is that patients with pulmonary fibrosis have had their reflux symptoms treated more aggressively as suggested by the fact that patients with pulmonary fibrosis were more frequently on acid suppressants. It would be worth assessing in future studies oesophageal involvement in specific patient groups with pulmonary fibrosis, for example patients with dcSSc who are SCL-70 negative and in whom epithelial injury is more strongly implicated or patients with lcSSc, ACA positive. Furthermore, it is worth exploring specific autoantibody/disease subtype association with site-specific gut involvement, rather than overall gut involvement.

One of the major limitations of using a subjective symptom questionnaire is that this may not accurately depict actual disease activity and severity. Previous studies have shown that asymptomatic patients did have abnormal oesophageal motility when investigated [28], so disease activity may actually have been underestimated using subjective measures. Furthermore, patients were often on drugs such as proton pump inhibitors, prokinetics and laxatives as treatment for their GI symptoms. On the other hand, GI symptoms may occur irrespective of actual SSc gut involvement, as for example bloating is often a symptom of irritable bowel syndrome, a condition occurring in up to 20% of the Western population, especially women [29]. Additionally, some of the drugs used commonly in SSc patients can have significant GI side effects such as mycophenolate, bisphosphonates, opiates and antibiotics.

One of the main drawbacks of this questionnaire is that it is using symptom frequency only and not severity to assess symptom burden, unlike other QOL questionnaires. In view of the multi-organ GI involvement and the variety of symptoms, the frequency of these is as indicative of symptom burden. Furthermore, Khanna et al. [18] showed that the SSc–GIT 1.0 scales were able to discriminate the self-rated severity of GI symptoms and found a significant association between this questionnaire and other QOL questionnaires such as the short form (36) health survey and health assessment questionnaire (SHAQ) [30].

Another limitation of this questionnaire is that there are some key symptoms that are not explored adequately, for example faecal incontinence [31, 32]. The questionnaire is also rather too long and would be quite time-consuming if it was to be used on a regular basis to monitor disease progression. A shorter version of this questionnaire has now been developed [33]. Ideally, objective measurements or tests to assess GI involvement should be used but these tests are often invasive and although more accurate in diagnosing GI involvement in scleroderma they are probably less useful in assessing disease progression. While treatment for GI involvement remains symptomatic a dedicated GI questionnaire gives an accurate assessment of symptom burden and can be used to assess this at different times and be used as a guide to adjust treatment.

In summary, patients with SSc have an extremely high burden of both upper and lower gut symptoms. There is no strong association of gut symptoms with other organ involvement or disease profile. The degree of symptoms demonstrated is more than would be expected from the symptoms documented in the clinical notes suggesting that patients usually under-report these symptoms. This is regrettable since many of the symptoms may be amenable to treatment and we would recommend routine assessment of GI symptoms.

### Rheumatology key messages

- GI involvement in SSc is common and associated with significant morbidity.
- There is no association of gut involvement with specific disease subtype.
- GI-focussed questionnaire is an effective way to assess gut symptoms and adjust treatment.
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References