Concise report

Gastrointestinal motility disorder assessment in systemic sclerosis

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Abstract

Objectives. SSc is a clinically heterogeneous and generalized disease, characterized by thickness of the connective tissue of the skin and internal organs, such as the digestive tract, impairing gastrointestinal (GI) motility. Our aim is to evaluate retrospectively abnormalities of oesophageal motility, gastric emptying, oro-cecal transit time (OCTT) and small intestine bacterial overgrowth (SIBO) in a large cohort of SSc patients.

Methods. Ninety-nine SSc patients were included in the study. Forty-two patients underwent oesophageal conventional manometry, 45 performed a [13C]octanoic acid breath test to measure gastric emptying time and all 99 patients performed a lactulose breath test in order to evaluate OCTT and SIBO. Data were compared with healthy controls.

Results. In SSc patients, median lower oesophageal sphincter (LOS) pressure [14 mmHg (25th–75th; 8–19) vs 24 mmHg (19–28); P < 0.01] and median wave amplitude [30 mmHg (16–70) vs 72 mmHg (48–96); P < 0.01] were lower than in controls. Oesophageal involvement, defined as reduced LOS pressure and ineffective oesophageal motility pattern, was encountered in 70% of SSc patients. A delayed gastric emptying time was present in 38% of SSc patients: mean $t_{1/2}$ was 141 ± 79 min vs 90 ± 40 min of controls ($P < 0.01$). Also, OCTT was significantly delayed in SSc: median OCTT was 160 min (25th–75th; 135–180) vs 105 min (25th–75th; 90–135) of controls ($P < 0.01$). SIBO was observed in 46% of SSc compared with 5% of controls ($P < 0.01$).

Conclusion. GI involvement is very frequent in SSc patients. Oesophagus and small bowel are more frequently impaired, whereas delayed gastric emptying is less common.

Key words: systemic sclerosis, scleroderma, gastrointestinal motility, oesophageal manometry, 13C-octanoate breath test, lactulose breath test.

Introduction

SSc is a chronic disease characterized by thickness of the connective tissue of multiple organs including the gastrointestinal (GI) tract in ~80% of the cases [1, 2]. Oesophageal manifestations with gastro-oesophageal reflux, dysphagia and heartburn are the most frequent GI complaints, and serious complications can occur in 50% of SSc patients [2, 3].

Following the oesophagus, the small intestine is the most common GI target involved in SSc, determining in these patients pseudo-obstructive crises and malabsorption with vomiting, abdominal pain, distension, anorexia...
and diarrhoea [4]. The impairment of intestinal motility leads to stasis of luminal contents and secondary small intestine bacterial overgrowth (SIBO) in up to 50% of patients [4–7]. In clinical practice, glucose and lactulose H2/CH4 breath tests represent valid and reliable diagnostic tools to diagnose SIBO [8–10].

The most frequent clinical manifestations of SSc gastric involvement are early postprandial fullness, bloating, nausea and vomiting, which can be documented in ~50% of patients by scintigraphy or using a [13C]octanoic acid breath test (OBT) [11–13]. The latter one represents a safe, simple and validated tool to measure gastric emptying [14, 15].

The aim of this study was to retrospectively evaluate abnormalities of oesophageal motility, gastric emptying and oro-cecal transit time (OCTT) in a large cohort of ambulatory SSc patients referring to two Italian tertiary centres in comparison with healthy subjects.

**Patients and methods**

This was a retrospective cohort study of 99 ambulatory patients with SSc whose diagnosis was based on literature criteria [16, 17]. Demographic and clinical data of SSc patients are shown in Table 1.

Forty-two patients underwent oesophageal conventional manometry, 45 performed OBT to measure gastric emptying time and the whole group of 99 patients was assessed by lactulose breath test (LBT) in order to evaluate OCTT and SIBO prevalence. Patients underwent the above examinations independently of the presence of GI complaints. Patients were compared with 60 healthy controls (mean age 57 ± 10 years; M/F 10/50) who underwent the three examinations as part of other studies [3, 7, 18–21]. All patients and controls provided written informed consent according to the Declaration of Helsinki. The study has been approved by local ethics committee (Ethics Committee of Azienda Ospedaliera Universitaria San Martino di Genova).

**Oesophageal manometry**

Oesophageal manometry was performed using an eight-lumen, water-perfused, oesophageal manometry catheter (Mui Scientific, Canada) assembly consisting of four radial ports and four lateral ports spaced 5 cm apart and radially orientated 120° with respect to each other, according to our methodology [20, 22]. We measured lower oesophageal sphincter (LOS) pressure, peak contraction amplitude, duration of contraction, coordination and propagation of velocity after swallows. The following normal values were considered: median LOS pressure, 24 mmHg (25th–75th; 19–28); median peristaltic wave amplitude, 72 mmHg (25th–75th; 48–96) and presence of <10% non-propagated wet swallows.

**Lactulose hydrogen breath testing**

The details of methodology of breath test preparation and performance have been previously described [7, 18, 18–]

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**Table 1** Demographic and clinical characteristics of SSc patients enrolled

<table>
<thead>
<tr>
<th>Demographic and clinical parameters</th>
<th>SSc patients</th>
<th>Healthy controls</th>
<th>P-value</th>
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<tbody>
<tr>
<td>Patients, n</td>
<td>99</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>Female/male patients, n</td>
<td>89/10</td>
<td>50/10</td>
<td>0.2302</td>
</tr>
<tr>
<td>Age, mean (s.d.), years</td>
<td>59 (11)</td>
<td>57 (10)</td>
<td>0.8307</td>
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<tr>
<td>Characteristics of SSc disease</td>
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<tr>
<td>Disease duration &gt;5 years from first non-RP symptom, n (%)</td>
<td>87 (87)</td>
<td>57 (10)</td>
<td>0.4807</td>
</tr>
<tr>
<td>Disease duration &lt;5 years from first non-RP symptom, n (%)</td>
<td>12 (12)</td>
<td>57 (10)</td>
<td>0.0307</td>
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<tr>
<td>SSc subtype</td>
<td></td>
<td></td>
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<tr>
<td>SSc diffuse, n (%)</td>
<td>31 (31)</td>
<td>57 (10)</td>
<td></td>
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<tr>
<td>SSc limited, n (%)</td>
<td>68 (68)</td>
<td>57 (10)</td>
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<tr>
<td>Major extra-intestinal organ involvement</td>
<td></td>
<td></td>
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<tr>
<td>Arthralgia/arthritis, n (%)</td>
<td>34 (34)</td>
<td>57 (10)</td>
<td></td>
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<tr>
<td>Digital pitting scars, n (%)</td>
<td>68 (68)</td>
<td>57 (10)</td>
<td></td>
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<tr>
<td>Cardiac dysfunction, a n (%)</td>
<td>8 (8)</td>
<td>57 (10)</td>
<td></td>
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<tr>
<td>Pulmonary dysfunction, a n (%)</td>
<td>23 (23)</td>
<td>57 (10)</td>
<td></td>
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<tr>
<td>Kidney dysfunction, a n (%)</td>
<td>9 (9)</td>
<td>57 (10)</td>
<td></td>
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<tr>
<td>Antibody pattern SSc related</td>
<td></td>
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<tr>
<td>ACA, n (%)</td>
<td>40 (40)</td>
<td>57 (10)</td>
<td></td>
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<tr>
<td>Anti-Scl 70 antibody, n (%)</td>
<td>29 (29)</td>
<td>57 (10)</td>
<td></td>
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<tr>
<td>Patients on anti-reflux therapy, n (%)</td>
<td>75 (75)</td>
<td>57 (10)</td>
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</tbody>
</table>

**Notes:**
aPulmonary hypertension (n = 4), ventricular dysfunction (n = 1), pericardial effusion (n = 1), auricular and/or ventricular arrhythmias (n = 2). bInterstitial lung disease (n = 17), reduced carbon monoxide diffusing capacity (n = 18) and restrictive or obstructive pattern at spirometry (n = 2118). cInterstitial nephritis (n = 1), ANCA-associated glomerulonephritis (n = 2) and reduced renal functional reserves (n = 9) manifested by proteinuria, microalbuminuria or isolated reduction in glomerular filtration rate. No patient had scleroderma renal crisis.
Breath 13CO2 was analysed by isotope-ratio mass spectrometry [19]. Breath was collected at time 0 and 15 min after the administration of an oral loading dose of lactulose (10 g in 120 ml of water). Alveolar air samples were collected in a 750 ml two-bag system and immediately underwent gas chromatographic analysis. OCTT is defined as the increase in the lactulose bolus reaches the cecum and was measured by gas chromatography (Quintron MicroLizer model DPplus, Milwaukee, WI, USA) in basal conditions and every 15 min for at least 4 h after the OBT. OCTT is the time the lactulose bolus reaches the cecum and was defined as the increase >10 ppm of H2/CH4 excretion compared with baseline in three consecutive air samples.. Breath testing was performed after an overnight fasting. Breath was collected at time 0 and every 15 min after the end of the test meal up to 4 h. Breath 13CO2 was analysed by isotope-ratio mass spectrometer and 13CO2 excretion curves were fitted according to a non-linear regression model [19]. The t½ (half emptying time) was calculated according to the Ghoos method [14]. Our normal median OCTT measurement was 105 min (25th-75th; 90-135), with 150 min as the upper limit of normal.

[13C]octanoate breath testing
The OBT was performed using the test meal EXPIROGer (Sofar SpA, Milan, Italy), a ready-to-eat, gluten- and lactose-free, 100 g muffin meal containing 100 mg of [13C]octanoic acid. Total energy intake was 378 kcal (61%), 14 g fats (33%) and 6 g proteins (6%). Breath testing was performed after an overnight fasting. Breath was collected at time 0 and every 15 min after the administration of an oral loading dose of lactulose (10 g in 120 ml of water). Breath was collected at time 0 and every 15 min after the end of the test meal up to 4 h. Breath 13CO2 was analysed by isotope-ratio mass spectrometer and 13CO2 excretion curves were fitted according to a non-linear regression model [19]. The t½ (half emptying time) was calculated according to the Ghoos method [14]. Our normal median OCTT measurement was 105 min (25th-75th; 90-135), with 150 min as the upper limit of normal range.

Statistical analysis
Quantitative variables were expressed as mean (±s.d.) or median and interquartile range (25th-75th) when needed. The Mann–Whitney test was used to compare quantitative variables between patients and controls and among different subgroups. A significance level of 0.05 was used in statistical tests. Statistical analysis was performed by means of SPSS software, version 12 for Windows (SPSS Inc., Chicago, IL).

Results
Details of GI involvement in SSc patients are shown in Table 2.

Oesophageal assessment
Globally, an abnormal oesophageal involvement was defined as reduced LOS pressure and ineffective oesophageal motility pattern was encountered in 70% of SSc patients, whose median LOS pressure [14 (8-19) vs 24 mmHg (19-28)] and wave amplitude [30 (16-70) vs 72 mmHg (48-96)] were significantly lower compared with controls (P < 0.01). Median LOS pressure and wave amplitude were not significantly different in relation to limited or diffuse cutaneous involvement: 14 (8-18) and 30 mmHg (20-70) vs 14 (9-20) and 30 mmHg (15-70) (P = 0.824 and P = 0.6906, respectively). Moreover, no differences were found between patients positive for ACA compared with negative ones [11 (8-16) and 23 (1-68) vs 17 (9-24) and 45 (20-73); P = 0.0910 and P = 0.2038, respectively] and patients positive for anti-topoisomerase I antibodies compared with negative ones [14 (8-18) and 15 (12-22) vs 30 (16-78) and 20 (16-50); P = 0.5145 and P = 0.4543, respectively].

Table 2. Details on GI involvement of SSc patients enrolled

<table>
<thead>
<tr>
<th>GI parameters</th>
<th>SSc patients</th>
<th>Healthy controls</th>
<th>P-value</th>
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<tbody>
<tr>
<td>Oesophageal assessment by means of conventional oesophageal manometry (n = 42)</td>
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<tr>
<td>Oesophageal dysfunction, n (%)</td>
<td>70 (70)</td>
<td></td>
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<tr>
<td>Median basal LOS pressure (25th-75th), mmHg</td>
<td>14 (8-19)</td>
<td>24 (19-28)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>LOS relaxation, %</td>
<td>100</td>
<td>100</td>
<td>1</td>
</tr>
<tr>
<td>Median distal contraction amplitude (25th-75th), mmHg</td>
<td>30 (16-70)</td>
<td>72 (48-96)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Patients with normal peristaltic, n (%)</td>
<td>16 (38)</td>
<td>56 (93)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Patients with ineffective oesophageal motility, n (%)</td>
<td>26 (62)</td>
<td>4 (7)</td>
<td>&lt;0.01</td>
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<tr>
<td>Gastric emptying assessment by means of OBT (n = 45)</td>
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<tr>
<td>Delayed gastric emptying, n (%)</td>
<td>38 (38)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean t½ (s.d.), min</td>
<td>140 ± 78</td>
<td>90 ± 40</td>
<td>&lt;0.01</td>
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<tr>
<td>Small bowel and SIBO assessment by means of an LBT (n = 90)</td>
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<tr>
<td>SIBO prevalence, n (%)</td>
<td>47 (46)</td>
<td>3 (5)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Prolonged OCTT, median (IQR), min</td>
<td>160 (135-180)</td>
<td>105 (90-135)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>
Gastric emptying assessment
A delayed gastric emptying time (t½ > 130 min) was present in 17 out of 45 SSc patients (38%). The mean t½ was 140 ± 78 min, which was significantly delayed compared with controls (90 ± 40 min; P < 0.01). Moreover, the median t½ was 126 min (93–158) in 36 patients with limited and 101 min (74–155) in 9 patients with diffuse cutaneous disease (P = 0.5513). No differences were found comparing patients positive for ACA with those negative [123 (99–135) vs 127 (86–135); P = 0.7023], patients positive for topoisomerase I antibodies with those negative [127 (93–135) vs 123 (87–135); P = 0.8645] and patients with different disease duration [134 (95–214) vs 115 (87–155); P = 0.4269].

Small bowel and SIBO assessment
The median OCTT was significantly longer in SSc patients than in controls: 150 min (135–180) vs 105 min (90–135); P < 0.01. Sixty-three out of 100 SSc patients (63%) had an OCTT longer than 150 min. Median OCTT was 150 min (130–180) in patients with limited and 165 min (150–180) in those with diffuse cutaneous disease (P = 0.0580). Patients with a disease duration of <5 years showed a lower OCTT than those with a disease duration of >5 years: 133 (116–150) vs 165 min (138–180); P < 0.0068. Finally, no differences were also found comparing patients positive for ACA with those who were negative [158 (135–180) vs 150 (135–180); P = 0.7906] and patients positive for topoisomerase I antibodies with those negative [150 (135–180) vs 160 (135–165); P = 0.8084]. LBT showed a double-peak profile, compatible with SIBO diagnosis, in 47 out of 99 SSc patients (46%) compared with 3 out of 60 controls (5%) (P < 0.01). Proton pump inhibitor (PPI) consumption was associated with a higher occurrence of SIBO (PPI users with SIBO 35 vs PPI non-users with SIBO 12; P < 0.01).

Discussion
GI involvement is very frequent in patients suffering from SSc, with up to 80% of patients complaining of GI symptoms [22–24]. In this study, we evaluated the incidence of GI involvement in a large cohort of SSc patients in order to define their GI impairment and suggest some minimal invasive or non-invasive diagnostic examinations potentially useful for physicians in clinical practice.

We found oesophageal abnormalities in 70% of patients, thus confirming the literature data of 75% of patients suffering from oesophageal impairment, mainly characterized by impaired peristalsis and low to absent LOS pressure [25–27]. In particular, the lower median wave amplitude is the most frequent detected abnormality (62%), followed by lower LOS pressure. A correlation between the severity of oesophageal disease and that of SSc has not been definitively demonstrated. Bassotti et al. [28] observed a direct relationship between scleroderma subsets and the severity of oesophageal motor impairment, even without a correlation between symptoms and the severity of manometric abnormalities. Our study did not find a significant difference between limited and diffuse patterns of the disease, while other studies, evaluating a larger patient sample, were able to find a significant difference in the amplitude and the length of distal peristaltic wave in groups of patients with more advanced disease, but they did not find a statistically significant difference in the prevalence of manometric LOS abnormalities among groups stratified by disease severity.

According to the existing literature showing a gastric dysfunction in 40–50% of cases [29–33], we confirm an incidence of delayed gastric emptying time of 38%. Although several techniques have been used to evaluate gastric motility alterations in SSc, we used OBT, a non-invasive, easy to perform and safe method that has been demonstrated to be more objective than other non-invasive techniques (i.e. ultrasonography). This probably explains why our SSc patients have a gastric emptying time significantly slower than controls, in disagreement with other non-invasive techniques [29]. So far, OBT seems to be a useful and promising tool in the assessment and follow-up of gastric involvement in SSc patients.

In medical literature, SSc patients report lower GI symptoms in 30% of cases [34] and, accordingly, we found the presence of SIBO, assessed by LBT, in 47% of our patients. Marie et al. [35] demonstrated a SIBO prevalence of 43.1% in a cohort of 51 patients by H2/CH4 glucose breath test (GBT) and therefore, LBT and GBT show a comparable sensitivity in patients with SSc. We chose to perform LBT instead of GBT to have the possibility to also study the OCTT, which was slower in SSc patients than in controls, confirming our previous results [7] in a larger cohort of patients. Moreover, we observed that patients with disease duration <5 years showed a lower OCTT than those with duration >5 years, suggesting that bowel motility worsens with progression of the disease.

Overall, these data confirm the importance of assessment of GI involvement in clinical management of patients with SSc. In particular, assessment of oesophageal motility seems to be a fundamental diagnostic step in all patients suffering from SSc. OCT seems to be a promising new non-invasive method to assess gastric emptying time. The SIBO prevalence is high in SSc patients and LBT seems to be a reproducible tool in its assessment, although the specificity and sensitivity are lower than those of GBT, unless in this disease, as our results showed. In this study, we did not evaluate SSc symptoms and then it was not possible to assess the possible correlation between them and SIBO. However, a previous study of our group [7] has demonstrated that SIBO therapy is able to beneficially affect symptoms in SSc patients.

The retrospective design of our study may potentially have led to overestimation of the percentage of patients with GI involvement. However, it is important to underline that all SSc patients were primarily evaluated by internal medicine physicians and they underwent GI examinations independently of GI complaints, thus reducing the influence of the above bias.
Future larger prospective studies are needed to confirm these results even with an accurate symptom collection and correlation with the described motility parameters. Moreover, it would be interesting to compare results from studies held in tertiary and non-tertiary centres in order to investigate the impact of different study populations on GI motility alterations and symptoms.

**Rheumatology key messages**

- The oesophagus is the most frequently involved organ in SSc, followed by small bowel and stomach.
- Small intestinal bacterial overgrowth affects almost half of SSc patients in our study.
- Breath tests could be useful tools in the assessment of gastrointestinal impairment in SSc.

**Disclosure statement:** The authors have declared no conflicts of interest.

**References**


