Internal anal sphincter atrophy in patients with systemic sclerosis

Nora M. Thoua1, Alexis Schizas1, Alastair Forbes2, Christopher P. Denton3 and Anton V. Emmanuel1

Abstract

Objectives. SSc is a connective tissue, multisystem disorder of unknown aetiology. The gastrointestinal tract (GIT) is affected in up to 90% of patients. The exact pathophysiology of GIT involvement is not known, but it is related to both neurogenic and myogenic abnormalities as well as possible vascular and ischaemic changes. Thinning of the internal anal sphincter (IAS) has been demonstrated in SSc with faecal incontinence. We aimed to investigate anal sphincter structure in patients with SSc.

Methods. Forty-four SSc patients [24 symptomatic (Sx) and 20 asymptomatic (ASx)] and 20 incontinent controls (ICs) were studied. Patients underwent anorectal manometry and endoanal US.

Results. In the ICs, external anal sphincter defects were more common, but the IAS was less atrophic, evident by both atrophy scores and IAS thickness. There was no significant difference in atrophy scores [Sx: 2 (1.5–3) vs ASx: 2 (1–2)] or IAS thickness [Sx: 1.85 (1.5–2.3) vs ASx: 1.8 (1.7–2.25)] between the Sx and ASx SSc patients.

Conclusion. Patients with SSc (both Sx and ASx) have thin and atrophic IAS, suggesting that IAS atrophy develops even in ASx patients and this may be amenable to treatment with sacral neuromodulation.

Key words: Internal anal sphincter, Atrophy, Faecal incontinence, Systemic sclerosis, Endoanal ultrasound, Anorectal involvement.

Introduction

SSc is a connective tissue disorder of unknown aetiology characterized by excess collagen deposition, chronic inflammation and vascular changes that affect multiple organs [1]. The gastrointestinal tract (GIT) is affected in up to 90% of patients [2]. The exact pathophysiology of GIT involvement is not known, but it is related to both neurogenic and myogenic abnormalities as well as possible vascular and ischaemic changes [3–5]. Histologically, the main changes seen in the GIT are smooth muscle atrophy and varying degrees of fibrosis as the disease progresses [6]. Oesophageal involvement is most common and upper gastrointestinal (GI) symptoms are frequently reported [7, 8]. Lower GI involvement can lead not only to constipation and evacuation difficulty but also diarrhoea and faecal incontinence. The anorectum is affected in 50–70% of patients with SSc, with >20% of patients developing faecal incontinence [9, 10].

In healthy subjects, faecal continence is maintained by the coordinated function of pelvic floor, rectum and the anal sphincters. The smooth muscle internal anal sphincter (IAS) is primarily responsible for the anal resting tone, contributing ~85% of the anal resting pressure. The striated external anal sphincter (EAS) makes a small contribution towards the resting anal pressure, but is primarily responsible for the voluntary contraction of the anal sphincter [11]. Disruption or weakness of the IAS typically leads to passive faecal incontinence, whereas that of the EAS leads to urge faecal incontinence [12, 13]. The IAS, being a smooth muscle, is more likely to be affected in SSc [14] and it has been suggested that the changes are similar to those seen in the lower oesophageal sphincter (LOS).

The existing literature, none of which includes more than 18 patients with SSc, suggests that the IAS is thinned and hyperechoic on US in the majority of patients with
SSc and faecal incontinence [15–17], although some patients may have a thickened hypoechoic sphincter, most likely secondary to collagen deposition [18]. Whether these differences relate to disease subtype or duration has not been addressed. Even less is known about patients with SSc and no faecal incontinence. If the pattern is similar to that seen in oesophageal involvement, we would expect to see structural and functional changes even in the absence of symptoms. This study aimed to quantify the sonographic changes in the anal sphincters of patients with SSc with and without faecal incontinence. We hypothesized that defects in the sphincter mechanism would be less common in incontinent SSc patients than in incontinent controls (ICs) without SSc. We further hypothesized that atrophic sphincter changes would occur more often in symptomatic (Sx) than asymptomatic (ASx) SSc patients.

Methods

Patients

Forty-four patients with SSc, 24 Sx (with anorectal symptoms) and 20 ASx (without anorectal symptoms) patients, were recruited to the study. Twenty patients, age and sex matched to the Sx SSc patients, referred to our GI physiology unit for investigations of faecal incontinence, were used as ICs. All patients gave informed consent to participate in the study, which was approved by the University College Hospital research ethics committee. Incontinence was assessed by using the Wexner incontinence score, a validated questionnaire assessing incontinence based on frequency and stool consistency.

Questionnaires

SSc patients were asked to complete the following questionnaires on the day of their assessments.

(i) Scleroderma GI tract 1.0 questionnaire: a 52-item self-completed instrument that provides a profile for GI symptoms in five broad categories and their effect on social and emotional well-being.

(ii) Short form-36 (SF-36) general health questionnaire: a multi-purpose, short-form health survey with 36 questions that yields an eight-scale profile of functional health and well-being scores.

(iii) EuroQol: a six-item self-completed instrument that provides a simple descriptive profile for health status by asking if the patient has no problems, some problems or significant problems in domains of: mobility, self-care, usual activities, pain/discomfort and anxiety/depression (scoring 1, 2 or 3, respectively).

Anorectal manometry

No bowel preparation was given before testing. An eight-channel radial water-perfused manometry system with a perfusion rate of 0.6 ml/min (MMS, Enschede, The Netherlands) was utilized. A latex-free balloon with 500 ml capacity was attached at the end of the manometry catheters (Ardmore Healthcare Limited, Amersham, UK, external diameter 3.9 mm). With the subject in the left lateral position, the station pull-through technique was employed to assess anal canal length, anal resting pressure and anal squeeze pressure.

Endoanal US

Endoanal US (EAUS) was performed to assess the integrity of anal sphincters and possible presence of sphincter infiltration and atrophy. A conventional Hitachi EUB 8500 US machine was used with an EUP R54AW-19 endoanal probe covered with a lubricated condom was inserted into the anus with the patient in the prone position. Conventional anal endosonography was performed according to a standard technique [18]. Images of the anal sphincters were taken at proximal, mid- and distal canal levels. Images were acquired by a trained radiographer and assessed independently by two experts. The anal sphincter complex was examined and the integrity and atrophy of the internal and external sphincters were described as follows, and scored 1–3 for analysis purposes [19].

Integrity

Integrity score: 1 = intact, 2 = focal thinning and 3 = defect/sca; focal thinning: thinning in muscle thickness, but fibres in continuity; and defect/sca: discontinuity of muscle fibres with or without replacement by lower echogenicity scar tissue.

Atrophy

Atrophy score: 1 = normal, 2 = mild atrophy, 3 = severe atrophy; mild internal sphincter atrophy: abnormal increased echogenicity and/or measurement 1.5–2 mm; severe internal sphincter atrophy: measurement <1.5 mm; mild external sphincter atrophy: muscle structure visible but abnormal high echogenicity suggestive of fatty replacement; and severe external sphincter atrophy: muscle structure very poorly or not defined suggestive of marked fatty replacement.

The IAS was measured at the level of greatest thickness at the 3, 6, 9 and 12 o’clock positions and the average thickness was calculated.

Statistics

Statistical analysis was performed using GraphPad Prism. As some of the values measured were non-normally distributed, results are expressed as median and interquartile range. The non-parametric Mann–Whitney and Kruskal–Wallis tests were used for comparisons of two and three groups, respectively. Correction for multiple comparisons was done using the Dunn’s correction.

Results

Patients

Forty-four SSc patients were studied. Twenty-four patients were Sx, reporting faecal incontinence, and 20 patients were ASx. Sex- and age-matched patients with
incontinence were used as controls. Table 1 summarizes the demographics and incontinence scores of the three patient groups. The median disease duration was 5.5 and 10.5 years for ASx and Sx patients, respectively. Five (25%) ASx patients and 4 (17%) Sx patients had disease duration of ≤3 years. There was no significant difference in the percentage of oesophageal symptoms between Sx and ASx SSc patients. Unfortunately, oesophageal manometry results were available for only two patients, and therefore we could not assess for correlation between abnormal oesophageal and anorectal manometry. Incontinence scores were higher in the IC and Sx groups compared with the ASx group. Although many patients reported both urge and passive faecal incontinence, urge incontinence was more common in the IC group (16/20 IC vs 12/24 SSc Sx patients). SSc patients more commonly reported passive incontinence or soiling (20/24 patients). Parity was higher in the IC group. Table 2 summarizes the quality-of-life questionnaire scores in SSc patients.

**Table 1** Demographic characteristics of three patient groups and disease characteristics of the SSc patients

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>ASx SSc</th>
<th>Sx SSc</th>
<th>ICs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (IQR)</td>
<td>57.5 (53.5–65.5)</td>
<td>61 (53–66)</td>
<td>50.5 (44–64)</td>
</tr>
<tr>
<td>Female : male ratio</td>
<td>20:0</td>
<td>20:4</td>
<td>20:0</td>
</tr>
<tr>
<td>Parity, median (IQR)</td>
<td>1 (0–2)</td>
<td>2 (1–2)</td>
<td>2 (2–3.5)*</td>
</tr>
<tr>
<td>Wexner incontinence, median (IQR)</td>
<td>2 (0.5–3.5)</td>
<td>10 (8–16)*</td>
<td>14 (11.5–16)*</td>
</tr>
<tr>
<td>Disease duration, median (IQR)</td>
<td>5.5 (3.3–11)</td>
<td>10.5 (4.5–18)</td>
<td>N/A</td>
</tr>
<tr>
<td>lcSSc/dcSSc, n</td>
<td>13/7</td>
<td>20/4</td>
<td>N/A</td>
</tr>
<tr>
<td>Autoantibodies, n (%)</td>
<td>ACA</td>
<td>8 (40)</td>
<td>17 (71)</td>
</tr>
<tr>
<td></td>
<td>SCL-70</td>
<td>2 (10)</td>
<td>3 (13)</td>
</tr>
<tr>
<td>Internal organ involvement, n (%)</td>
<td>Pulmonary</td>
<td>5 (25)</td>
<td>10 (42)</td>
</tr>
<tr>
<td></td>
<td>Cardiac</td>
<td>1 (5)</td>
<td>2 (8)</td>
</tr>
<tr>
<td></td>
<td>Renal</td>
<td>2 (10)</td>
<td>2 (8)</td>
</tr>
<tr>
<td></td>
<td>Oesophageal</td>
<td>14 (70)</td>
<td>23 (96)</td>
</tr>
</tbody>
</table>

Comparisons made using Mann–Whitney and Kruskal–Wallis tests. *P < 0.05 compared with ASx. IQR: interquartile range.

**Table 2** Questionnaire scores in SSc patients

<table>
<thead>
<tr>
<th>Questionnaires</th>
<th>ASx SSc, median (IQR)</th>
<th>Sx SSc, median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SF-36</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total score</td>
<td>62.43 (54.45–77.84)</td>
<td>54.01 (39.74–73.57)</td>
</tr>
<tr>
<td>Physical health score</td>
<td>60.4 (42.8–75.1)</td>
<td>50.8 (27–68.5)</td>
</tr>
<tr>
<td>Mental health score</td>
<td>65.15 (53.95–70.9)</td>
<td>62.35 (35.63–72.95)</td>
</tr>
<tr>
<td>EuroQol (EQ-5D)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mobility</td>
<td>1 (1–2)</td>
<td>1 (1–2)</td>
</tr>
<tr>
<td>Self-care</td>
<td>1 (1–1.5)</td>
<td>1 (1–2)</td>
</tr>
<tr>
<td>Usual activities</td>
<td>1 (1–2)</td>
<td>2 (1–2)</td>
</tr>
<tr>
<td>Pain/discomfort</td>
<td>1.5 (1–2)</td>
<td>2 (2–2)</td>
</tr>
<tr>
<td>Anxiety/depression</td>
<td>1 (1–2)</td>
<td>2 (1–2)</td>
</tr>
<tr>
<td>VAS score</td>
<td>80 (60–80)</td>
<td>62 (53–80)</td>
</tr>
<tr>
<td>SSc-GIT 1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reflux</td>
<td>92.6 (81.5–96.5)</td>
<td>55.6 (42.55–77.75)*</td>
</tr>
<tr>
<td>Distension</td>
<td>83.3 (72.2–94.35)</td>
<td>50 (36.1–63.85)*</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>100 (77.7–100)</td>
<td>61.1 (27.75–100)*</td>
</tr>
<tr>
<td>Constipation</td>
<td>100 (77.7–100)</td>
<td>66.65 (22.2–100)*</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>100 (83.3–100)</td>
<td>66.7 (50–100)*</td>
</tr>
<tr>
<td>Social</td>
<td>100 (100–100)</td>
<td>81.7 (65–95)*</td>
</tr>
<tr>
<td>Emotional</td>
<td>100 (94.45–100)</td>
<td>55.6 (31.45–77.75)*</td>
</tr>
</tbody>
</table>

Comparisons made using the Mann–Whitney test. *P < 0.05. IQR: interquartile range; VAS: visual analogue scale.
group [IC: 42.2 (33–57.4) vs ASx: 63.8 (53.7–73.9); P < 0.05 vs Sx: 50.8 (40.7–61)]. The squeeze pressure was lower in the IC group, and below the normal range, compared with both the ASx and Sx groups [IC: 46.95 (30–63.9) vs ASx: 104.6 (81–128.3) vs Sx: 121.4 (101.3–141.6); P < 0.05 for both]. There was no significant difference in the resting or squeeze pressures between the ASx and Sx SSc patient groups. Subset analysis of patients with dcSSc and lcSSc did not show any difference in anorectal manometry nor IAS atrophy between the two subsets, although this analysis is limited by the small number of patients in each subset.

**EAUS**

SSc patients had more atrophic IAS sphincter (atrophy median score 2), but largely intact IAS and EAS compared with ICs. The age- and sex-matched ICs were more likely to have EAS defects; they also had less IAS atrophy, evidenced by both atrophy scores and IAS thickness. Figure 1 show the IAS atrophy scores and IAS thickness, respectively, in the three patient groups. Surprisingly, there was no significant difference in atrophy scores [Sx: 2 (1.5–3) vs ASx: 2 (1–2)] or IAS thickness [Sx: 1.85 (1.5–2.3) vs ASx: 1.8 (1.7–2.25)] between the Sx and ASx SSc patients. EAUS images of IAS atrophy and sphincter defects are seen in Fig. 2.

There was no significant correlation between incontinence scores and atrophy and integrity scores or IAS thickness. In subgroup analysis, there was a positive correlation between Wexner incontinence score and IAS atrophy in the SSc patient groups (r = 0.38, P = 0.01). There was no correlation between IAS thickness or IAS atrophy scores and disease duration in SSc patients.

**Discussion**

Anorectal involvement is reported in 50–70% of patients with SSc [10]. Faecal incontinence is probably under-reported in view of the stigmatizing nature of the symptom and its social implications. In an anonymous questionnaire study, 24% of patients reported faecal soiling [9]. As the anorectum is the second most commonly affected site of the GI tract, after the oesophagus, there have been a number of studies that investigated anorectal symptoms mainly with physiological measurements

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**Fig. 1** (A) IAS atrophy scores in the three groups. (B) IAS thickness in the three groups.

**Fig. 2** EAUS images showing (A) EAS and IAS defect (→), IAS (→), EAS (→) and (B) IAS atrophy (→).
such as anorectal manometry, sensation and reflexes. Typically, it is the smooth muscle IAS that is affected in SSc, thus resulting in lower resting pressure [20–23], whereas squeeze pressure is usually normal as the EAS is largely unaffected [20, 22–24]. In our study, we found slightly lower resting pressure in the Sx SSc patients when compared with the ASx patients, but the ICs had significantly lower resting pressures. This is probably a reflection of the presence of both internal and external sphincter defects in the latter group of patients. As in a number of previous studies, the squeeze pressure in the SSc patients was normal.

Although well recognized that the anal sphincters are likely to be affected in scleroderma, there are only few studies that have assessed the anal sphincter structure. Engel et al. [12] were the first to report morphological changes of the internal sphincter in SSc patients. They described two female patients with SSc and passive faecal incontinence with very thin, hyperrechoic IAS [14]. deSouza et al. [17], in an MRI study of 18 patients with SSc and 19 controls with and without incontinence, showed that the SSc patients with incontinence had thinner IASs than controls, but not in those without incontinence, suggesting that incontinence is related to smooth muscle atrophy in this group. They further found reduced gadolinium enhancement of the IAS in all SSc patients, suggesting an ischaemic origin of IAS atrophy. They did not find any significant difference in the EAS thickness in SSc patients [17]. Koh et al. [16] described 11 SSc patients with incontinence and suggested two distinct types of morphological changes in the IAS. Patients had either very thinned, difficult to delineate and hyperrechoic internal sphincters or, less commonly, a thickened, homogeneous and uniformly hyperrechoic IAS [16].

In our study, we aimed to investigate the morphology of anal sphincters in SSc patients. We compared SSc patients with and without anolectral symptoms and specifically faecal incontinence with controls that were being investigated for faecal incontinence. We showed that patients with SSc, both those with faecal incontinence and the ASx ones, had thinned and atrophic IAS compared with the ICs. In contrast, the ICs had more common evidence of EAS defects. We did not find any SSc patients with thickened IAS in our unselected sequential cohort of patients.

The gastrointestinal smooth muscle may be involved early in patients with SSc, before the onset of clinical symptoms. This is seen in the oesophagus where physiological, mainly motility abnormalities are seen even in patients with no oesophageal symptoms [25, 26]. The IAS shares similarities with the LOS in that they both are smooth muscle continuation of the circular muscle layer of the gut that maintains chronic tone. The oesophageal abnormalities in SSc are low basal LOS pressure resulting in loss of competence and also lack of peristalsis of the lower oesophageal body [27–29]. These abnormalities are thought to be secondary to collagen deposition, resulting in smooth muscle atrophy and fibrosis [30]. Although collagen deposition and smooth muscle atrophy are well recognized in GIT involvement in SSc, there is evidence that these abnormalities are preceded by vascular insufficiency and neural dysfunction [31, 32]. Vasculopathy of arterioles is common in SSc. Decreased oesophageal blood flow has been found in patients with RP and reduced gastric and duodenal blood flow has been demonstrated in SSc patients [31, 33]. In the anorectum, deSouza et al. [17] showed that SSc patients with faecal incontinence had reduced gadolinium enhancement of the IAS. The pathogenesis of neuropathy may be caused by compression of nerve fibres by collagen deposits or secondary to arteriolar changes in the vasa nervorum. Another possible mechanism is autoantibody related. Antibodies to muscarinic M3 receptors have been found to inhibit enteric cholinergic neurotransmission and to be associated with severe GI involvement [34–36]. The evidence of neuropathy in the anorectum comes from evidence of reduced sensation and more so by evidence of absent or impaired rectoanal inhibitory reflex (RAIR) found in ~70% of SSc patients with anorectal involvement [20, 22, 37]. Malandrini et al. [38] found evidence of nerve degeneration in rectal mucosa of SSc patients with faecal incontinence.

Oesophageal involvement is found in up to 90% of patients with SSc, and even patients with no oesophageal symptoms when investigated are found to have oesophageal dysmotility [29, 39]. Only a small number of SSc patients with no anolectral symptoms have been investigated and therefore there are little data on anolectral physiology abnormalities in ASx SSc patients. deSouza et al. [17] studied four SSc patients without incontinence and did not find reduced IAS thickness as found in the SSc incontinent patients. We found that although SSc continent patients did not have reduced resting pressure, they did have IAS atrophy and reduced IAS thickness. Although different imaging modalities were used in these two studies, MRI and EAUS, this is unlikely to account for the difference in findings as the relationship between the two modalities for IAS and EAS thickness is excellent [40]. It is possible that this early finding of IAS atrophy may be secondary to vascular or neurological dysfunction and not secondary to fibrosis, which tends to occur later in the disease process. Confirmation of such a hypothesis requires histological evidence from full thickness biopsy, which is not ethically justifiable. Interestingly, a histological study of oesophageal tissue in SSc patients and controls found smooth muscle atrophy in 94% of SSc patients and only 5% of controls. The pathological findings seemed to be either secondary to loss of neural function or a primary smooth muscle lesion [41]. We have previously found reduced anal sensation and impaired RAIR in this ASx SSc patient group, suggestive of a neural cause for those changes [42]. These findings are significant with regard to management of anolectral symptoms as it is possible that sacral neuromodulation [15] may be more successful than other therapies and that it may be worth considering early, minimal treatment of Sx or even ASx patients, if anolectral physiology abnormalities are present.
In summary, we have shown that patients with SSc have thin and atrophic IAS. This finding is evident in both Sx and ASx patients and development of symptoms seems to be dependent on other factors. With the development of better treatments such as sacral neuromodulation, screening for anorectal dysfunction may be worth considering.

### Rheumatology key messages

- Anorectal involvement is common in SSc and evident even in ASx patients.
- The IAS is thin and atrophic in SSc patients.
- Development of faecal incontinence is multifactorial.

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