Original Research Article

JSRD Journal of Scleroderma and Related Disorders

Journal of Scleroderma and Related Disorders
1–8

DOI: 10.1177/23971983241288039
journals.sagepub.com/home/jso
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An evaluation of autonomic and gastrointestinal symptoms, and gastric emptying, in patients with systemic sclerosis

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Abstract

Objective: Assessment of gastrointestinal and autonomic symptoms in patients with systemic sclerosis, and possible associations with gastric emptying rate.

Methods: Participant and patient disease-related characteristics were collected. Gastrointestinal and autonomic symptoms were assessed by the UCLA-SCTC GIT 2.0 and COMPASS-31 questionnaires, respectively. Potentially confounding gastrointestinal medications were discontinued where possible. Gastric emptying was assessed using a non-radioactive ^{13}C sodium acetate isotope, end-expiratory breath samples collected at baseline and then serial timepoints up to 120 min.

Results: In total, 49 participants were studied: 17 with systemic sclerosis with variable gastrointestinal involvement, and healthy matched (n = 17) and non-matched controls (n = 15), the last to control for the impact of age rather than disease on gastric emptying and autonomic function. The total mean (range) UCLA GIT 2.0 questionnaire for patients with systemic sclerosis was 0.63 (0.0–1.5) and for both healthy matched and non-matched controls was 0.04 (0.0–0.2), and was higher in patients with systemic sclerosis across all domains. The total mean (range) COMPASS-31 score for patients with systemic sclerosis patients was 32.2 (0.0–54.9) and for healthy matched- and non-matched controls: 7.45 (0.0–24.9) and 4.25 (0.0–2.1), respectively, again higher for patients with systemic sclerosis across all domains. No association was observed between patients' UCLA GIT 2.0 total score ($s = -0.039$, $p = 0.38$), total COMPASS 31 score ($s = -0.108$, $p = 0.68$), or COMPASS-31 GI domain ($s = -0.051$, $p = 0.85$) and gastric emptying rates.

Conclusion: Gastrointestinal and autonomic symptoms are overrepresented in patients with systemic sclerosis but did not associate with gastric emptying rates.

Keywords

Systemic sclerosis, scleroderma, gastrointestinal, autonomic dysfunction, gastric emptying

Date received: 2 August 2024; accepted: 13 September 2024

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Key messages

- Gastrointestinal (GI) and autonomic symptoms are common and heterogeneous in systemic sclerosis (SSc) and can be substantial.
- There was no association observed between GI or autonomic symptoms and gastric emptying rates.

Introduction

The gastrointestinal (GI) tract is almost universally (>90%) affected in systemic sclerosis (SSc) during the course of the disease and significantly impacts on quality of life and function. It is also an important cause of disease-related mortality.[1–10] The aetiopathogenesis of SSc is complex and likely multifactorial, including (but not limited to) aberrant tissue fibrosis, vasculopathy and abnormalities of the (both innate and adaptive) immune system, which drive the development of widespread organ dysfunction, including the GI tract.[3,11]

A major challenge in clinical practice is that GI involvement in patients with SSc is highly heterogenous, including within individual patients, both anatomically and over time.[12] GI motility is dysfunctional in SSc, and the manifestations are diverse, including (but not limited to) gastro-oesophageal reflux disease, gastroparesis, intestinal pseudo-obstruction, small intestinal bacterial overgrowth, malabsorption and intestinal failure, potentially requiring parenteral nutrition.[3,4,7]

The autonomic nervous system (ANS) has been implicated in the pathogenesis of GI disease in SSc, particularly in the development GI dysmotility.[7,13] Autonomic dysfunction has been reported to be common in patients with SSc.[14,15] For example, in the study by Adler et al.,[15] which sought to quantify the burden of autonomic symptoms in 101 consecutive patients with SSc as assessed by the Composite Autonomic Symptom Score (COMPASS 31) questionnaire, the mean score was higher (24.9 ± 15.5) compared to previously published healthy controls (8.9 ± 8.7). Furthermore, those with significant GI disease had higher scores across several domains compared to those with either absent or mild GI manifestations.[15]

Slower gastric emptying has been reported to occur commonly in SSc compared to normal subjects.[16,17] For example, Marie et al.[16] studied 57 consecutive individuals with SSc who underwent ^{13}C-octanoic acid breath testing and observed that the prevalence of delayed gastric emptying was 47.4%. Furthermore, a significant association was observed between a global score of patients' GI (including upper and lower) symptoms and the presence of delayed gastric emptying.[16] Similarly, in a study which included 45 participants with SSc who completed a ^{13}C-octanoic acid breath test,[18] delayed gastric emptying was observed in over four-fifths (n=38). However, autonomic symptoms per se were not assessed in these studies, a gap that therefore required bridging via the current study.

Against this background, the aim of our study was to assess for the presence of GI and autonomic symptoms in patients with SSc, and the possible association of these with measured gastric emptying rate.

Methods

Study overview

Participants were recruited at a specialised referral centre for SSc. Pragmatically (and reflecting 'real-world' clinical practice), we sought to recruit SSc patients with a spectrum of GI involvement associated with the disease and without the use of a specified purposeful sampling or recruitment approach. Our intention (based on an initial sample size calculation) was to recruit 20 with SSc, 20 age- ($\pm$5 years)/gender-matched healthy participants and 15 non-age/gender-matched healthy participants. We specifically included a non-matched group with a lower mean age to control for any potential confounding effects of age rather than disease being responsible for any autonomic symptoms reported in older healthy individuals or for age-related changes in gastric emptying. Participants with a clinical diagnosis of SSc were subdivided into those with diffuse cutaneous or limited cutaneous subtypes according to the study by LeRoy et al.[18] The study was granted ethical approval by the North West Ethics Committee (13/NW/0423) and all subjects signed informed consent.

Patient and disease-related demographics

For patients with SSc, relevant personal- and disease-related demographics were recorded. SSc disease-onset was defined as the first non-Raynaud's phenomenon (RP) clinical feature.[18] Height and weight were recorded (wearing light clothing), and body mass index (BMI) was calculated.

Confounding medication

Participants with SSc were asked to stop taking any medications potentially affecting gastric emptying for the duration of five half-lives prior to their attendance, with medications omitted for 2–7 days (as relevant): for medications prescribed for GI symptoms – proton pump inhibitors (PPIs): 7 days; histamine H2 receptor antagonists: 3 days, prokinetics: 2 days and alginates: 12 h. Patients who were unable to stop medications for RP were excluded. Participants unable to stop GI medications were still recruited as the effects of these medications on gastric emptying were considered minimal, and there was a clear need to include some patients with GI involvement. The study was rescheduled if participants had used any potentially confounding non-prescription medications including (but not limited to) antitussives, antihistamines and opioid analgesics, within 3 days prior to the study.[19]

Table 1. Patient and matched/non-matched healthy controls demographics.

	SSc	Matched healthy controls	Non-matched healthy controls
Number (n)	17	17	15
Male: female (n)	1:16	1:16	4:11
Mean age (range, years)	63.2 (45.1–77.3)	62.2 (45.3–75.1)	36.3 (23.0–59.8)
Smokers: non-smokers (n)	1:16	1:16	2:13
Mean BMI (n, range)	24.4 (19.0–33.3)	25.7 (19.0–32.7)	27.1 (18.4–45.8)

Healthy participants

Healthy controls had no history of RP or SSc, autonomic dysfunction or delayed gastric emptying. No healthy participants were taking confounding medication.

Gastrointestinal and autonomic questionnaires

We used the University of California at Los Angeles (UCLA)-Scleroderma Clinical Trial Consortium Gastrointestinal Tract (GIT) 2.0 questionnaire to assess the frequency of any GI symptoms over the preceding 7 days.[20] The questionnaire consists of 34 items encompassing seven multi-item scales: reflux, distension/bloating, diarrhoea, faecal soilage, constipation, emotional well-being and social functioning, and a total GIT score can be calculated to assess health-related quality of life and the severity of GI symptoms in patients with SSc.[20,21] The score ranges from 0 to 2.83 (most severe).[20]

We applied the COMPASS-31 tool[22] to determine the presence of autonomic dysfunction symptoms.[22] The questionnaire consists of 31 questions examining six weighted domains: orthostatic intolerance, vasomotor dysfunction, secretomotor dysfunction, GI dysfunction (including constipation, diarrhoea and gastroparesis), urinary dysfunction and pupillomotor dysfunction. In general, the questions evaluate patients' symptoms over the previous year, apart from one question in the vasomotor domain which examines symptoms (related to perspiration) in the preceding 5 years.[22] A higher score (range 0–100) indicates greater autonomic dysfunction.

Gastric emptying

We used a stable, water-soluble, non-radioactive ^{13}C sodium acetate (100 mg powder) isotope. Prior to each study, this was weighed on scales calibrated to 1 mg and mixed with Ensure® immediately prior to drinking. We selected this as it is in widespread use in clinical practice and easy to consume. This was important as the oral and oesophageal problems seen in SSc would be potential issues for patients with the solid meals used in scintigraphy studies, and it is more of physiological use in a nutrient rich meal rather than just the acetate isotope in solution. End-expiratory breath samples were collected before consuming the test drink, and then at 5, 10, 20, 30, 40, 60, 80, 100 and 120 min. Samples were collected using 100 mL double-ended breath sample bags, and a one-way mouthpiece prevented air from escaping before the stopper was placed. Normal values have not been defined for this test meal and therefore, our analysis was based on comparisons with our healthy control groups.

Statistical methods

Differences between group means for demographics and symptoms (UCLA GIT 2.0 and COMPASS 31) were assessed using the Mann–Whitney U tests. For patients, correlations (Spearman's) were also assessed between GI symptoms and gastric emptying, and between GI symptoms. The differences between the three participant groups' gastric emptying results were assessed using either the Kruskal–Wallis or Mann–Whitney U tests. For all statistical analyses, a significant difference was considered as a p-value of less than 0.05. Analyses were conducted using SPSS (version 22).

Results

Patients and matched/non-matched healthy controls

Patient and matched/non-matched healthy control demographics are presented in Table 1. Of 46 potentially eligible individuals (from a previous study, n = 170),[23] 17 with SSc were recruited. The majority had limited cutaneous systemic sclerosis (lcSSc; n = 16) and half (n = 8) were anticentromere antibody-positive. The median (range) duration of RP and SSc was 196 (16–653) and 115 (12–348) months, respectively. They had a wide range of GI disease severity as determined by the Medsger disease severity scale:[24] normal (41%), mild (53%) and moderate (6%). None were classed as severe. Most (n = 12) received treatment with a PPI, and 5 were unable to discontinue it. Three were taking drug therapy (two nifedipine, one losartan) for RP, but omitted these within the required time period to participate in the study. No patients were prescribed prokinetics. In total, 17 healthy matched and 15 healthy non-matched controls were recruited.

Table 2. UCLA GIT 2.0 questionnaire domains. Data are presented as the comparison of means.

Symptom domain	SSc Mean (range) (n = 17)	Matched healthy controls SSc Mean (range) (n = 17)	Non-matched healthy controls SSc Mean (range) (n = 15)	SSc versus matched healthy controls (p)	SSc versus non-matched controls (p)	Matched versus non-matched controls (p)
Reflux	0.60 (0.0–2.0)	0.04 (0.0–0.4)	0.06 (0.0–0.5)	<0.01	<0.01	0.71
Distension/bloating	1.12 (0.06–3.0)	0.19 (0.0–1.0)	0.13 (0.0–1.0)	<0.01	<0.01	1.00
Faecal soilage	0.35 (0.0–1.5)	0.00 (0.0–0.0)	0.00 (0.0–0.0)	0.02	0.02	1.00
Diarrhoea	0.35 (0.0–1.5)	0.03 (0.0–0.5)	0.00 (0.0–0.0)	0.02	0.01	0.79
Social functioning	0.39 (0.0–1.0)	0.00 (0.0–0.0)	0.00 (0.0–0.0)	<0.01	<0.01	1.00
Emotional well-being	0.71 (0.0–2.1)	0.00 (0.0–0.0)	0.00 (0.0–0.0)	<0.01	<0.01	1.00
Constipation	0.63 (0.0–2.5)	0.07 (0.0–1.0)	0.00 (0.0–0.0)	<0.01	<0.01	0.58
Total GI score	0.63 (0.0–1.5)	0.04 (0.0–0.2)	0.04 (0.0–0.2)	<0.01	<0.01	0.79

Gastrointestinal symptoms as assessed by the UCLA GIT 2.0 questionnaire

The total mean (range) UCLA GIT 2.0 questionnaire for participants with SSc was 0.63 (0.0–1.5) and for both healthy matched and non-matched controls, it was identical at 0.04 (0.0–0.2). Across all of the domains, the mean UCLA GIT 2.0 domain scores were significantly higher for those with SSc compared to healthy matched and non-matched controls (Table 2). There were no significant differences observed between healthy matched and non-matched controls.

Autonomic symptoms as assessed by the COMPASS-31 questionnaire

The total mean (range) COMPASS-31 score for patients with SSc was 32.2 (0.0–54.9) and for healthy matched and non-matched controls was 7.45 (0.0–24.9) and 4.25 (0.0–2.1), respectively. The mean COMPASS-31 scores across all domains for patients with SSc were significantly higher compared to healthy matched or non-matched controls (Table 3). With the exception of the GI domain, there was no difference observed for the other five domains between healthy matched and non-matched controls (although most healthy group participants scored low).

Gastric emptying

Only one participant with SSc was unable to drink the entire Ensure meal, and results were incomplete for three healthy participants (one matched and two non-matched). Area under the curves (AUC) were not calculated for these three healthy participants due to missing data points. For all participant groups, gastric emptying rates increased over the first hour, peaking at approximately 100 min, and with the greatest differentiation at approximately 80–100 min (Figure 1(a)).

The mean (SD) AUC (Figure 1(b)) for patients with SSc was $43.8 \pm 21\%$ ^{13}Cdose/hour (range 8.5–94.0) and for healthy matched and non-matched controls was 68.9 ± 16.2 (range 39.8–86.2) and 58.8 ± 25.2 (range 26.8–103.0), respectively. The matched controls' AUC significantly differed from patients ($p < 0.01$), but not from the non-matched healthy controls ($p = 0.11$). Nor did AUC differ significantly between participants with SSc and non-matched healthy controls ($p = 0.06$).

Gastrointestinal and autonomic symptoms versus gastric emptying rate

No association was observed between patients' UCLA GIT 2.0 total score ($s = -0.039$, $p = 0.38$) (Figure 2(a)), total COMPASS 31 score ($s = -0.108$, $p = 0.68$) (Figure 2(b)) or COMPASS-31 GI domain ($s = -0.051$, $p = 0.85$) (Figure 2(c)), and gastric emptying rates.

Discussion

The key novel strength of our study is that we investigated the relationships between GI symptoms and autonomic dysfunction, and assessed this with an objective assessment of gastric emptying.

Across all of the domains, the mean UCLA GIT 2.0 and COMPASS-31 were significantly higher for patients with

Table 3. COMPASS 31 domains. Data are presented as the comparison of means.

Symptom domain	SSc mean (range) (n = 17)	Matched healthy controls mean (range) (n = 17)	Non-matched healthy controls mean (range) (n = 15)	SSc versus matched healthy controls	SSc versus non-matched healthy controls	Matched versus non-matched healthy controls
Orthostatic	9.88 (0.0–24.0)	0.15 (0.0–2.5)	0.0 (0.0–0.0)	0.05	0.05	1.00
Vasomotor	3.33 (0.0–4.2)	0.15 (0.0–2.5)	0.0 (0.0–0.0)	<0.01	<0.01	0.79
Secretomotor	5.17 (0.0–12.9)	0.50 (0.0–4.3)	0.0 (0.0–0.0)	<0.01	<0.01	0.41
GI	9.72 (0.0-25.0)	2.89 (0.0–7.1)	1.25 (0.0–4.5)	<0.01	<0.01	0.03
Bladder	2.22 (0.0–16.7)	0.26 (0.0–1.1)	0.0 (0.0–0.0)	0.01	<0.01	0.26
Pupillomotor	1.96 (0.0–5.0)	0.82 (0.0–2.7)	0.60 (0.0–2.7)	<0.01	<0.01	0.48
Total	32.2 (0.0–54.9)	7.45 (0.0–24.9)	4.25 (0.0–22.1)	<0.01	<0.01	0.11

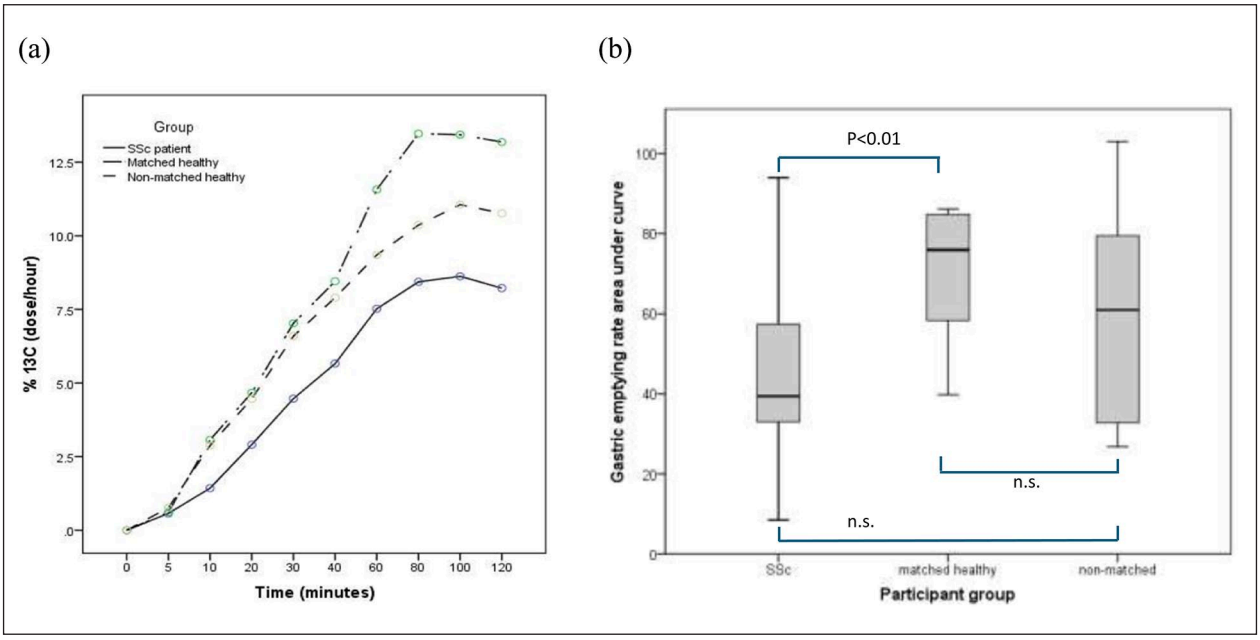

Figure 1. Gastric emptying between the participant groups. (a) Mean gastric emptying rates (% 13^C dose/hour). (b) Box-and-whisker plot of gastric emptying area under the curve. There was a significant difference between the patients and matched healthy controls. n.s. not significant.

SSc compared to healthy matched and non-matched controls as anticipated. Going further, our study went on to assess for any link between autonomic scores and abnormal physiology, using gastric emptying as a surrogate readout. There were no significant associations observed between the total GI and autonomic scores and gastric emptying rates. This is in contrast to previous studies including Marie et al.,[16] and a study which included 71 patients with SSc and GI symptoms who underwent whole gut (assessing the oesophagus to colon) transit scintigraphy, in which modest associations were observed between reflux symptoms and delayed gastric emptying ($r=-0.32$, $p=0.05$),[12] Neither of these earlier studies evaluated the burden of autonomic symptoms alongside an objective gastric emptying study. Furthermore, in a more recent, larger study by Alvarez-Hernandez et al.,[25] symptoms of global dysautonomia were observed in up to one-third of patients with SSc and GI involvement. Of interest, GI

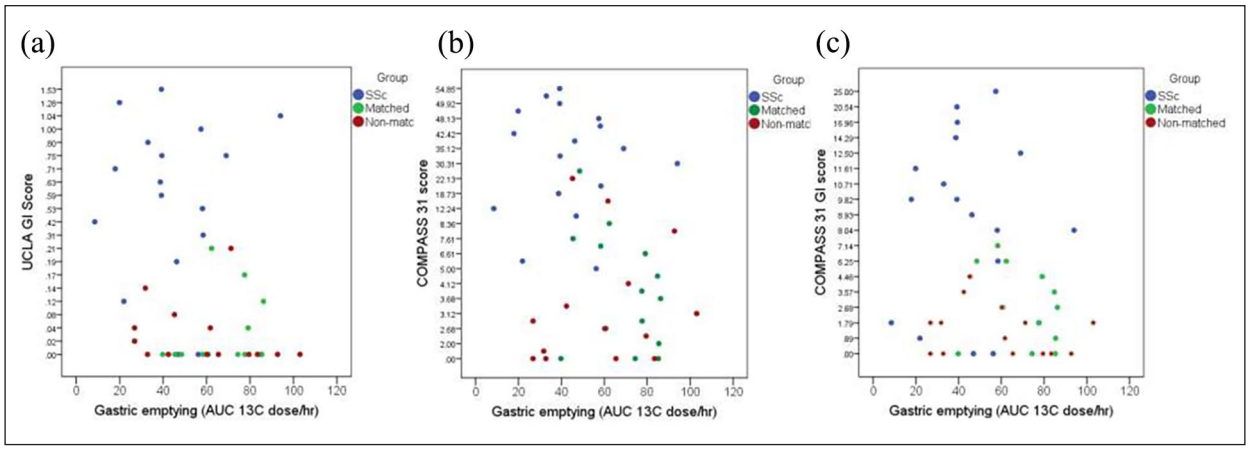

Figure 2. A: Gastric emptying rates compared to gastrointestinal and autonomic symptoms. (a): Total UCLA GIT 2.0 score. (b): Total COMPASS-31 score. (c): COMPASS-31 GI domain.

(gastric and colonic) transit, as assessed by measured whole-gut scintigraphy, was faster in those patients with 'global' autonomic dysfunction (which the authors defined as ⩾ 5 positive COMPASS-31 subdomains).[25] In addition, upper GI involvement was associated with higher (total) COMPASS-31 scores.[25]

The total mean COMPASS-31 score in our study for participants with SSc was 32.2, comparable to the study by Adler et al.[15] (24.9). We were not studying severely affected patients or overt gastroparesis in which gastric emptying will be slow by definition but a population with milder GI symptoms yet a significant burden of other autonomic symptoms. Indeed, the overall total UCLA GIT 2.0 score and individual domains (except distension/bloating) were numerically low, although it is important to highlight that there was a wide range in the individual participant scores, including some with more significant symptoms.

Our study benefitted from the novel inclusion of a healthy unmatched control group to assess whether any of the autonomic issues identified were possibly a consequence of ageing, which is known to have a negative impact on autonomic function rather than SSc, rather than disease. We utilised widely used questionnaires to assess GI (UCLA GIT 2.0) and autonomic (COMPASS-31) symptoms. This is of relevance because it is well reported that females are more commonly affected by dysautonomia-related conditions, including people with SSc.[15]

An important limitation is the relatively small number of participants which were included. Ours could be considered as a small pilot study, that the patient population was heterogenous and was not comprehensively defined in terms of GI motility. Although the initial recruitment targets were not met, there would have been futility in continuing to recruit as the symptom scoring component was already highly significant, but there was no prospect of the physiological aspects achieving significance. Therefore, it was deemed appropriate by the study investigators to cease recruitment. However, it could be argued that this detracted from the power of our study to identify an association with upper GI dysmotility and symptoms of dysautonomia.

In conclusion, our data support the expectation that GI and autonomic symptoms are highly overrepresented in participants with SSc, compared to healthy controls. Our study adds value as it includes accounting for the impact of ageing on autonomic symptoms. However, we did not observe any association between GI or autonomic symptoms and gastric emptying rate in our study. Pivotally, we suggest that normal gastric emptying studies should not be interpreted to exclude autonomic or symptomatic GI dysfunction. Another important consideration is the high proportion of patients with the limited subset of the disease (and again, the relatively small number of studied patients), which may have influenced our findings (e.g. these patients often have the most stable GI disease over time compared to those with diffuse disease).[26] It should be noted that there is a growing current awareness of the disutility of gastric emptying studies in other areas of neurogastrointestinal medicine.

Future (larger) studies are required including inclusion of larger numbers of people with SSc, especially those of younger age and shorter disease duration, ideally off potentially confounding medication for study, and additional more advanced functional assessment of the GI tract, for example, by physiological MRI scanning,[27] and incorporation of novel (e.g. anti-muscarinic-3 acetylcholine receptor) autoantibodies.[28] Taken together, the development of novel approaches to diagnosis of GI dysfunction, an improved understanding of pathophysiology including obtaining definite conclusions about the role of autonomic dysfunction, will hopefully lead to the development of effective treatment strategies for GI involvement in SSc.

Data availability statement

The data underlying this article will be considered to be shared on reasonable request to the corresponding author.

Declaration of conflicting interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: M.H. received none. E.H. was funded by the Raynaud's and Scleroderma Association. A.L.H. received consultancy fees from Arena, Boehringer Ingelheim, Camurus, Galderma and Gesynta Pharma, speaker fees from Janssen and research funding from Gesynta Pharma. S.L. and J.T.M. received none.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: We appreciate the support of participating patients and the Medical Physics Department at Salford Royal NHS Foundation Trust for developing the in-house autonomic function analyser. This work was supported by the NIHR Manchester Biomedical Research Centre (NIHR203308). The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care. The Raynaud's and Scleroderma Association (now Scleroderma and Raynaud's UK) provided financial support for Dr Elizabeth Harrison's Doctoral Research Fellowship.

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The statement

The Editor/ Editorial Board Member of JSRD is an author of this article; therefore, the peer review process was managed by alternative members of the Board and the submitting Editor/Board member had no involvement in the decision-making process.

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