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The Relationship between Autonomic Dysfunction of the Gastrointestinal Tract and Emotional Distress in Patients with Systemic Sclerosis

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Abstract

Background/Objectives: We hypothesized that emotional distress in systemic sclerosis (SSc) patients with moderate to severe gastrointestinal (GI) dysfunction is associated with dysautonomia. We sought to determine: (1) the clinical characteristics associated with emotional distress in SSc, (2) the odds of having dysautonomia in those with emotional distress, and (3) whether GI dysautonomia, as measured by the Survey of Autonomic Symptoms (SAS), correlates with GI dysautonomia on the Composite Autonomic Symptom Scores-31 (COMPASS-31).

Methods: Clinical and demographic features from our prospective cohort study were compared among SSc patients with and without GI-associated emotional distress (UCLA SCTC GIT 2.0 well-being subscale >0.5 or ≤0.5) in cross-sectional analysis. Covariates/confounders independently associated with emotional distress were used to construct multivariable logistic regression models. The COMPASS-31 and SAS GI subdomains were compared with Spearman's correlation.

Results: 46 patients with SSc were enrolled in the study. In univariate analyses, age (OR 1.06, p=0.026), severity of GI dysautonomia (COMPASS-31: OR=1.41, p=0.003), anti-CENP (A/B) antibodies (OR=3.60, p=0.044), and anti-PM-Scl (75/100) antibodies (OR 0.15, p=0.035) were associated with emotional distress. In the adjusted model, those with more severe GI dysautonomia remained more likely to have emotional distress (OR=1.85, p=0.026); those with anti-PM-Scl (75/100) antibodies were less likely to have emotional distress (OR=0.03, p=0.031). The SAS and COMPASS-31 GI subdomains moderately correlated (ρ=0.68, p <0.001).

Conclusions: In SSc, increased symptom burden related to GI dysautonomia is associated with emotional distress. Multidisciplinary approaches addressing both the physical and emotional needs of the SSc patient may be warranted to optimize patient care.

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Keywords

Systemic Sclerosis; Autonomic Dysfunction; Emotional Distress; Gastrointestinal Dysfunction; Patient-Reported Outcomes

I. Introduction:

Anxiety and depression are prevalent in systemic sclerosis (SSc), affecting approximately half of all patients[1],[2]. SSc patients with anxiety and depression have greater global disability as well as poor self-esteem and avoidance coping strategies[3]. Emotional distress is sub-optimally recognized and treated in patients with SSc, and multidisciplinary approaches to improve coping and manage symptoms provide benefit in improving quality of life.[4]

In SSc, depressive symptoms and anxiety have been associated with GI tract dysfunction as well as overall disease activity.[5, 6] Depressed mood according to the Center for Epidemiologic Studies Short Depression scale (CES-D-10) has been associated with worse total University of California at Los Angeles Scleroderma Clinical trial Consortium Gastrointestinal Tract 2.0 (UCLA SCTC GIT 2.0) scores as well as GI scale scores (except fecal soilage) in a cohort of SSc patients.[7] Similarly, SSc patients with GI dysfunction were found to have higher levels of anxiety and depression compared to those who did not have GI dysfunction based on the Patient-Reported Outcomes Measurement Information System-29 (PROMIS®−29) instrument.[8] While the role of mental health and GI dysfunction in SSc has not been extensively studied, patients with Irritable Bowel Disease (IBD) and psychological comorbidity with increased GI symptom-reporting have better outcomes with treatment of both psychological and physical symptoms.[9] Antidepressants have some beneficial effect for mood-disorders related to IBD, but multi-disciplinary approaches that focus on coping skills and self-management have achieved better responses.[10-13]

Autonomic dysfunction, or vagal nerve dysfunction, is associated with a sympathetic/parasympathetic nervous system imbalance and is thought to contribute to GI dysmotility in SSc.[14-18] Mechanistically, the vagus nerve also has a significant role in controlling both GI motility and the normal stress response.[19] A recent study by Adler et al. found that patients with SSc who had significant GI disease had more symptoms of dysautonomia as measured by the Composite Autonomic Symptom Scale-31 (COMPASS-31) survey compared to SSc patients who did not have these features[20]. Similarly, in a small observational study of German patients with SSc, 12 out of 36 patients with esophageal dysfunction had co-existent autonomic dysfunction (cardiac, pupillary)[17]. In other chronic diseases associated with autonomic dysfunction such as IBD, hypertension, and Parkinson's disease, anxiety levels were higher in patients with increased autonomic dysfunction.[21-26]

We hypothesized that autonomic dysfunction of the GI tract is more prevalent among SSc patients with emotional distress, and that more severe GI dysautonomia is associated with increased odds of emotional distress. We aimed to identify clinical features associated with this patient subgroup, as such patients may benefit from a multimodal treatment approach

focused on coping strategies to manage high GI symptom burden that may not be alleviated by traditional pharmacologic strategies alone. We also performed a preliminary assessment to determine whether the GI domains of the Survey of Autonomic Symptoms (SAS) and COMPASS-31 surveys correlate in SSc, as this may be a simpler alternative instrument when evaluating dysautonomia in future studies.

II. Materials and Methods

i. Patients:

All patients provided informed consent to participate in the Johns Hopkins Scleroderma Center cohort and met the 2013 American College of Rheumatology/European League Against Rheumatism criteria for systemic sclerosis. Patients were part of a prospectively enrolled GI cohort within the Scleroderma Center (GI Assessment Protocol cohort, a.k.a GAP, IRB# IRB00108366, NA_00034985) which included patients who met the following criteria: (1) symptoms of significant upper GI disease (Medsger score >1); or (2) symptoms of both lower and upper GI dysfunction refractory to standard doses of GERD medications (upper GI tract), and/or traditional over-the-counter medications (lower GI tract). Symptoms of upper GI dysfunction were defined as refractory GERD with or without dysphagia, early satiety, nausea/vomiting, and/or unintentional weight loss, while symptoms of lower GI dysfunction were defined as distension, bloating, diarrhea, and/or constipation. Patients with GI disease not attributed to systemic sclerosis by the treating physician were excluded. Patients were also excluded if they were unwilling or unable to participate in our protocoled GI studies or unable to provide informed consent.

ii. Clinical Phenotyping

Demographic and clinical variables were collected at the baseline research visit including age, sex, race, education, employment status, and medications (disease modifying agents (DMARDs), prednisone, anti-depressants/anxiolytics, sleep aids, benzodiazepines, and beta-blockers). Clinical characteristics included skin type (limited, diffuse), disease duration (defined as age at first Raynaud's or non-Raynaud's symptom), the subdomains of the Medsger's Disease Severity Score (MDSS), and the patient global assessment of disease activity from the scleroderma Health Assessment Questionnaire (sHAQ). Within the sHAQ, a visual analogue scale (VAS) (scored 0–3; 3 most severe) was used to evaluate the participant's global assessment of disease severity.

The Medsger severity score was used to assess SSc disease severity.[20, 27] Significant GI disease was previously defined as a MDSS ≥ 2, severe Raynaud's (RP) was defined by a MDSS ≥2.[20] Significant lung involvement was defined by a MDSS≥2, and any heart disease was defined by a MDSS ≥1. Synovitis, sicca symptoms, and arthralgia were binary variables and scored based on the presence or absence of characteristic at the time of the visit.

iii. Autoantibody Profile:

Antibodies were evaluated using a commercially available line immunoblot assay (Scleroderma [Nucleoli] Profile Euroline [IgG]; Euroimmun) which screens for the presence

of antibodies to Scl-70, centromere (CENP A or CENP B), RNA polymerase-3 (RP11 or RP155), fibrillarin (U3RNP), Ro52, and Pm-Scl (Pm-Scl-75 or Pm-Scl-100). Antibodies were considered positive if in moderate (++) to high titer range (+++).

iv. Transit Studies:

Scintigraphy-based comprehensive transit studies, which evaluate GI transit from the esophagus through the colon were performed within 9 months of the study visit date using previously defined parameters.[28] For the purposes of this study, we focused on the presence of delayed esophageal, gastric, and colonic emptying which are associated with autonomic dysfunction.[29]

v. Measurement Instruments:

All patients completed the UCLA SCTC GIT 2.0, COMPASS-31, and Survey of Autonomic Symptoms (SAS) on the same day within 6-months of the collection of the previously described clinical and demographic variables.

COMPASS-31 questionnaire- The 31-item COMPASS assessment tool (COMPASS-31) is a validated abbreviated version of the 164-item COMPASS tool that quantifies autonomic symptom severity across six domains.[30] COMPASS-31 domains include orthostatic intolerance (4 items), vasomotor dysfunction (3 items), secretomotor dysfunction (4 items), gastrointestinal dysfunction (12 items), bladder dysfunction (3 items), and pupillomotor dysfunction (5 items). Scoring across domains is weighted and totaled to derive an autonomic symptom score ranging from 0 to 100 (max score: orthostasis, 40; vasomotor, 5; secretomotor, 15; gastrointestinal, 25; bladder, 10; pupillomotor, 5). The gastrointestinal domain on the COMPASS-31, assesses gastrointestinal symptoms of dysautonomia and has been shown to have excellent test-retest reliability and internal validity.[30]

UCLA GIT 2.0- The GIT is a 34-item validated instrument that includes six subscales: reflux (8 items), distention/bloating (4 items), diarrhea (2 items), constipation (4 items), fecal soilage (1 items), emotional well-being (9 items), and social functioning (6 items).[31] The emotional well-being category specifically relates to GI symptoms, and higher scores correspond to lower levels of well-being (i.e. emotional distress; referred to as such throughout this text). Moderate emotional distress has been previously defined as a GIT severity score ≥0.50.[32]

Survey of Autonomic Symptoms (SAS)- The SAS is an 11-item (women) and 12-item (men) instrument validated in the diabetic neuropathy population with good internal consistency and reliability (Cronbach $\alpha = 0.76$).[33] The instrument addresses several autonomic symptom domains including orthostatic, sudomotor symptoms, vasomotor, gastrointestinal, urinary, and sexual dysfunction. The instrument is divided into two parts, the presence of a symptom and resultant severity score (1–5, 5 most severe), if present. Total impact scores range from 0–60 for men and 0–55 for women.

vi. Statistical analyses:

Patients were stratified based on low versus high emotional well-being according to the GIT 2.0 instrument (emotional well-being subscale GIT: low <0.5; high ≥0.5, higher scores indicate more emotional distress). Demographic and baseline clinical variables were compared between groups. To further evaluate symptoms specific to autonomic dysfunction, the mean and standard deviation of the COMPASS-31 subdomains were compared amongst low versus high levels of emotional distress using Pearson chi-squared tests. Scores from GI-specific questions on the SAS were also compared among patients with low versus high levels of emotional distress.

Univariate and multivariable logistic models were developed to determine the association between emotional distress, clinical characteristics, and the subdomains of the COMPASS-31 and SAS. The model was adjusted for demographic variables (age, disease duration) and for clinical variables that differed between groups ($p<0.1$) by chi-squared tests. Pearson's and Spearman's correlations were used to compare the subdomains of the GIT 2.0 as well as the gastrointestinal subdomains of the SAS and COMPASS-31 instruments.

STATA 15 (STATA Corporation, College Station, Texas) was used to perform the analyses. The protocol was approved by the Institutional Review Board at Johns Hopkins University School of Medicine (IRB00108366, NA_00034985).

III. Results:

i. Clinical and demographic characteristics of the scleroderma cohort

Forty-six patients with SSc and symptoms of gastrointestinal (GI) disease were recruited and completed the COMPASS-31, UCLA GIT 2.0., bloodwork, physical examination, and medication reconciliation. Among these patients, 81% were female, and 81% were white; 31% had diffuse SSc (Table 1). The mean (SD) age of included patients was 57 (11.5) years with mean (SD) disease duration of 13.9 (11.3) years; mean (SD) age at first symptom onset was 43.1 (15.2) years. Nearly half of patients were employed (48.9%), and 45.7% had a college degree or greater.

The majority (61%) of patients had significant GI disease (MDSS≥2). Transit studies were available on 40 individuals of which 89% demonstrated evidence of delayed GI transit. 55% (n=21) had delayed esophageal transit, 41% (n=19) had liquid or solid delayed gastric transit, 10% (n=4) had delayed small bowel transit, and 62% (n=24) had delayed large bowel transit.

Over half of patients had sicca symptoms (57%); 50% had significant lung disease (MDSS ≥2); 41% had heart disease (MDSS≥1); and 33% had severe RP (MDSS≥2). Nearly half of patients (46%) complained of arthralgia, with a small proportion of patients having synovitis (7%). Serologically, the majority of patients (52%) had anti-centromere (A/B) antibodies; patients with anti-Scl-70 antibodies (26%), anti-Ro-52 antibodies (24%), anti-PM-Scl (75/100) antibodies (17%), and anti-RNA polymerase III antibodies (9%) were also represented.

At the time of the survey, nearly all patients were taking medications for GERD: 81% of patients were taking proton pump inhibitors, 59% were taking H2 receptor blockers, and 27% were taking antacids. Current immunomodulatory agents used by patients included mycophenolate mofetil (27.9%) and methotrexate (9.3%). Cyclophosphamide, azathioprine, and IVIG were each used by fewer than 5% of individuals. Because the use of steroids can impact emotional distress, we examined the prevalence of steroid use in the GI population. We identified two patients who were taking steroids for inflammatory arthritis, and one patient who had recently completed a steroid burst for a pending procedure requiring contrast. These patients were relatively evenly distributed across the two groups, and their emotional scores were not outliers in the dataset, and therefore it is unlikely that the association between GI disease and emotional distress was driven by this factor. Current anti-depressant/anxiolytic usage was also evaluated, with 33% taking selective serotonin reuptake inhibitors/selective norepinephrine reuptake inhibitors (SSRI/SNRI); a small proportion of individuals were taking benzodiazepines (20%), tricyclic antidepressants (4%), and sleep-aids (17%). Current beta-blocker use, for various reasons, was noted in 20% of patients. Opioid use was noted in 11% of individuals.

ii. Cross-Sectional Univariate Analysis: SSc characteristics of patients with emotional distress

To determine whether emotional distress was associated with specific features of SSc, we compared the clinical and demographic characteristics of patients with high and low levels of emotional distress according to the UCLA GIT 2.0 Emotional Well-Being sub-domain. The baseline characteristics of subjects stratified by emotional distress are summarized in Table 1. Patients with high and low levels of emotional distress did not differ in terms of age, disease onset, disease duration, sex, race, education, employment, skin type, or smoking status (all p values <0.05), although there were trends towards an association with high emotional distress in older patients (p= 0.065) and patients with limited cutaneous disease (p=0.06). There was a trend for increased use of GERD medications (proton pump inhibitors, H2 blockers, and antacids) in those with high levels of emotional distress compared to low levels of emotional distress (96% vs 78%, p=0.05). Current use of other medications did not differ between groups including use of prednisone, methotrexate, mycophenolate mofetil, SSRI/SNRI, tricyclic anti-depressants, sleep-aids, benzodiazepines, or beta-blockers. Significantly more individuals with anti-centromere (A/B) antibodies were identified in the group with emotional distress compared to those without distress (64% vs 33%, p=0.040), and significantly fewer had anti-PM-Scl (75/100) antibodies (7% vs. 33%, p=0.022).

Baseline clinical characteristics did not differ between those with high and low levels of emotional distress including Medsger RP severity scores, Medsger lung severity scores, Medsger GI severity scores and delayed transit times, and the proportion of patients with arthralgia, synovitis, or Sicca symptoms (all p values>0.05) (Table 1). Mean pain scores on a visual analog scale (VAS) (mean 1.10 (SD, 0.84) vs 1.05 (SD, 0.82); p=0.85) and the patient global rating of disease activity (according to the sHAQ; mean 1.38 (SD, 0.86) vs 1.32 (SD, 0.79); p=0.80) did not differ between patients with high and low levels of emotional distress at baseline.

To determine if dysautonomia was more prevalent among those with emotional distress, we compared sub-domain scores from the COMPASS-31 between groups of patients with high and low levels of emotional distress. The COMPASS-31 gastrointestinal score was significantly worse in subjects with emotional distress compared to those without emotional distress (14.22, (SD, 4.29) vs 9.61 (SD, 2.7); p=<0.001). The other sub-domains of the COMPASS-31 did not differ between groups including orthostatics, pupillomotor, vasomotor, bladder, and secretory domains (Table 2; all p values>0.05). Similarly, in patients who completed the SAS (n=34), the SAS GI score was significantly worse in subjects with emotional distress compared to those without distress (6.9, (SD, 3.5) vs 3.1 (SD, 2.3); p=<0.001). There was also a trend towards an association between a higher total autonomic symptom severity score (SAS Column B) and emotional distress on the UCLA GIT 2.0 (p=0.062). The other sub-domains of the SAS did not significantly differ between those with high and low levels of emotional distress including orthostatics, sexual dysfunction, vasomotor, bladder, and secretomotor domains (all p values>0.05).

To identify the GI symptoms that correlated with emotional distress in SSc, we evaluated the subdomains of the GIT using a Pearson correlation matrix (Table 3). GIT emotional distress scores correlated the most with abdominal distension (r=0.49), followed by diarrhea (r=0.37), fecal soilage (r=0.33), reflux (r=0.29), and constipation (r=0.26). We also determined that the GI subdomains of the COMPASS-31 and SAS significantly correlated (ρ=0.68, p<0.001).

iii. Univariate Logistic Regression: Evaluating the association between dysautonomia and emotional distress

We then sought to quantify the association between emotional distress and dysautonomia. Using univariate logistic regression, older age (OR=1.06, p=0.049), anti-centromere (A/B) antibodies (OR=3.60, p=0.044), and GI dysautonomia (COMPASS-31) (OR=1.41, p=0.003) were associated with increased odds of emotional distress (Table 4). Anti-PM-Scl (75/100) antibodies negatively associated with emotional distress (OR 0.15, p=0.035). There was no significant association between emotional distress and cutaneous subtype or disease duration (p values<0.05).

iv. Multivariable Logistic Regression

After adjusting for relevant clinical variables and potential confounders, including age, disease duration, cutaneous subtype, and anti-centromere (A/B) antibodies, those with anti-PM-Scl antibodies (OR=0.03, p=0.031) had decreased odds of emotional distress, while those with GI dysautonomia (OR=1.85, p=0.026) had increased odds of emotional distress. Age and anti-centromere (A/B) antibodies were not associated with increased odds of emotional distress in this adjusted model (all p values >0.05). The GI subdomain of the SAS was also substituted in this multivariable logistic regression model, in which the relationship between GI dysautonomia and emotional distress was consistent (OR 1.64, p=0.022).

IV. Discussion:

In this SSc cohort (n=46) of patients with moderate to severe GI dysfunction, those with emotional distress (GIT 2.0) had a significantly greater degree of GI autonomic dysfunction compared to those without emotional distress; other domains of autonomic dysfunction were not significantly different for those with and without emotional distress. Similar findings were noted in the patient subset who completed the SAS (Table 2).

Of the many facets of GI dysfunction, GI dysautonomia specifically appears to have a distinct relationship with emotional distress. There previously has been controversy in the literature that somatic symptoms related to SSc may inflate the depression and anxiety rating scores depending on the measurement instrument used. Leavens et al. noted that the 9-item Patient Health Questionnaire (PHQ-9) for depression was 25% higher in SSc patients compared to an age-adjusted healthy general population.[34] This possibly suggested a small to moderate variance from somatic symptoms not related to depression. In our current analysis, we also present evidence that emotional distress is not necessarily related to underlying scleroderma disease severity, as the Medsger scores were not significantly different between groups (distress: mean (SD) 1.9 (0.7); no distress: mean (SD) 1.5 (0.7), p=0.12). Patients with and without emotional distress also did not have significantly worse RP, heart, or lung dysfunction according to the MDSS (Table 1). Additionally, patients with emotional distress did not have worse perception of disease activity compared to those without emotional distress (sHAQ: 1.32 (SD 0.79) vs 1.38 (SD 0.86)). Like treatment of IBD, this may suggest that patients with SSc and GI dysfunction may derive more benefit from multi-modal treatment approaches opposed to pharmacologic strategies only. Multidisciplinary approaches that include self-management and coping skills for high symptom burden and psychological comorbidity have shown benefit in IBD and other disorders of the autonomic nervous system.[13, 35-39]

Patients with high levels of emotional distress were more likely to use GERD medications than patients with low levels of emotional distress. This may reflect an association between GERD and emotional distress which was previously reported in the literature;[7] however, the association between emotional distress, GERD, and autonomic dysfunction has not previously been explored. We also noted that there were significantly more individuals with anti-centromere (A/B) positivity in the high emotional distress group and more individuals with anti-PM-Scl (75/100) positivity in the low emotional distress group (Table 1). We suspect that this may be attributable to the fact that anti-PM-Scl antibodies are associated with less overall GI involvement, and less severe GI involvement than patients with anti-centromere antibodies.[40] It is important to note that in this cohort of SSc patients, Medsger GI severity scores were not significantly different, and the relationship between antibody positivity and emotional distress may more specifically correspond to GI dysautonomia.

This study was novel in its use of the SAS as an assessment tool for autonomic dysfunction in a population of patients with systemic sclerosis. The GI components of the SAS and the COMPASS-31 were significantly correlated in our preliminary analysis (ρ=0.68, p<0.001). The SAS is a relatively brief survey when compared to the COMPASS-31 and should be

considered further in SSc as a simpler alternative instrument when evaluating dysautonomia in the future.

Our study has several strengths. To our knowledge, this is one of the first cross-sectional studies to evaluate emotional distress in patients with SSc with moderate to severe GI dysfunction and varying levels of severity of dysautonomia. Our SSc cohort is well-characterized in terms of clinical characteristics, antibody status, and GI dysfunction, in which dysautonomia has been evaluated by two different scoring instruments (COMPASS-31, SAS) and objective testing. Limitations of our study include: (1) a small sample size, which may restrict our ability to identify some differences between high and low emotional distress; (2) a relatively homogeneous cohort, in which the patients in our study were mostly white; it is unknown if race may play a role in this process; and (3) use of GI-specific instruments for the evaluation of emotional symptoms. Although the GIT 2.0 is not a dedicated measure to evaluate emotional health and specifically anchors to GI symptoms, the GIT emotional well-being domain has previously been cross-walked to the commonly used 10-item Centre for Epidemiological Studies Depression Scale (CES-D-10) [7] in SSc. Future studies to more specifically evaluate the relationship between generalized emotional distress and dysautonomia using additional psychometric instruments are warranted.

V. Conclusions:

In patients with SSc, patients with GI dysautonomia were more likely to have emotional distress related to GI symptoms. A multidisciplinary approach, including both pharmacologic and non-pharmacologic treatment modalities, focused on symptom management, is an important consideration for improving mental health in this subset of patients. Highly reliable and valid patient-reported outcome measurements, particularly those that specifically address anxiety and depression, will be important to implement in future SSc care and research.

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VI. References:

[1]. Amaral TN, Peres FA, Lapa AT, et al. Neurologic involvement in scleroderma: a systematic review. Semin Arthritis Rheum 2013; 43: 335–47. [PubMed: 23827688]

[2]. Nguyen C, Ranque B, Baubet T, et al. Clinical, Functional and Health-Related Quality of Life Correlates of Clinically Significant Symptoms of Anxiety and Depression in Patients with Systemic Sclerosis: A Cross-Sectional Survey. PLoS One 2014; 9: e90484. [PubMed: 24587375]

[3]. Del Rosso A, Mikhaylova S, Baccini M, et al. In Systemic Sclerosis, Anxiety and Depression Assessed by Hospital Anxiety Depression Scale Are Independently Associated with Disability and Psychological Factors. Biomed Res Int 2013; 2013: 1–8.

[4]. Almeida C, Almeida I, Vasconcelos C. Quality of life in systemic sclerosis. Autoimmun Rev 2015; 14: 1087–1096. [PubMed: 26212726]

[5]. Thombs BD, Taillefer SS, Hudson M, et al. Depression in patients with systemic sclerosis: A systematic review of the evidence. Arthritis Rheum 2007; 57: 1089–1097. [PubMed: 17665491]

[6]. Nietert PJ, Mitchell HC, Bolster MB, et al. Correlates of depression, including overall and gastrointestinal functional status, among patients with systemic sclerosis. J Rheumatol 2005; 32: 51–7. [PubMed: 15630725]

[7]. Bodukam V, Hays RD, Maranian P, et al. Association of gastrointestinal involvement and depressive symptoms in patients with systemic sclerosis. Rheumatology (Oxford) 2011; 50: 330–4. [PubMed: 20884655]

[8]. Kwakkenbos L, Thombs BD, Khanna D, et al. Performance of the Patient-Reported Outcomes Measurement Information System-29 in scleroderma: a Scleroderma Patient-centered Intervention Network Cohort Study. Rheumatology (Oxford) 2017; 56: 1302–1311. [PubMed: 28431140]

[9]. Gracie DJ, Williams CJM, Sood R, et al. Poor Correlation Between Clinical Disease Activity and Mucosal Inflammation, and the Role of Psychological Comorbidity, in Inflammatory Bowel Disease. Am J Gastroenterol 2016; 111: 541–51. [PubMed: 27002800]

[10]. Hall BJ, Hamlin PJ, Gracie DJ, et al. The Effect of Antidepressants on the Course of Inflammatory Bowel Disease. Can J Gastroenterol Hepatol 2018; 2018: 1–11.

[11]. McCombie AM, Mulder RT, Gearry RB. Coping Strategies and Psychological Outcomes of Patients with Inflammatory Bowel Disease in the First 6 Months After Diagnosis. Inflamm Bowel Dis 2015; 21: 1. [PubMed: 25489960]

[12]. Janmohamed N, Steinhart AH. Measuring Severity of Anxiety and Depression in Patients with Inflammatory Bowel Disease. Inflamm Bowel Dis 2017; 23: 1168–1173. [PubMed: 28613229]

[13]. Keefer L, Kane SV. Considering the Bidirectional Pathways Between Depression and IBD: Recommendations for Comprehensive IBD Care. Gastroenterol Hepatol (N Y) 2017; 13: 164–169. [PubMed: 28539843]

[14]. Hermosillo AG, Ortiz R, Dábague J, et al. Autonomic dysfunction in diffuse scleroderma vs CREST: an assessment by computerized heart rate variability. J Rheumatol 1994; 21: 1849–54. [PubMed: 7837149]

[15]. Ciftci O, Onat AM, Yavuz B, et al. Cardiac repolarization abnormalities and increased sympathetic activity in scleroderma. J Natl Med Assoc 2007; 99: 232–7. [PubMed: 17393947]

[16]. Di Ciaula A, Covelli M, Berardino M, et al. Gastrointestinal symptoms and motility disorders in patients with systemic scleroderma. BMC Gastroenterol 2008; 8: 7. [PubMed: 18304354]

[17]. Lock G, Straub RH, Zeuner M, et al. Association of autonomic nervous dysfunction and esophageal dysmotility in systemic sclerosis. J Rheumatol 1998; 25: 1330–5. [PubMed: 9676765]

[18]. Iovino P, Valentini G, Ciacci C, et al. Proximal stomach function in systemic sclerosis: relationship with autonomic nerve function. Dig Dis Sci 2001; 46: 723–30. [PubMed: 11330404]

[19]. Pavlov VA, Tracey KJ. The vagus nerve and the inflammatory reflex--linking immunity and metabolism. Nat Rev Endocrinol 2012; 8: 743–54. [PubMed: 23169440]

[20]. Adler BL, Russell JW, Hummers LK, et al. Symptoms of Autonomic Dysfunction in Systemic Sclerosis Assessed by the COMPASS-31 Questionnaire. J Rheumatol 2018; 45: 1145–1152. [PubMed: 29907667]

[21]. Engel T, Ben-Horin S, Beer-Gabel M. Autonomic Dysfunction Correlates with Clinical and Inflammatory Activity in Patients with Crohn's Disease. Inflamm Bowel Dis 2015; 21: 1. [PubMed: 25489960]

[22]. Jarrett ME, Burr RL, Cain KC, et al. Anxiety and depression are related to autonomic nervous system function in women with irritable bowel syndrome. Dig Dis Sci 2003; 48: 386–94. [PubMed: 12643620]

[23]. Carthy ER. Autonomic dysfunction in essential hypertension: A systematic review. Ann Med Surg 2014; 3: 2–7.

[24]. Bajkó Z, Szekeres C-C, Kovács KR, et al. Anxiety, depression and autonomic nervous system dysfunction in hypertension. J Neurol Sci 2012; 317: 112–116. [PubMed: 22425019]

[25]. Rutten S, Ghielen I, Vriend C, et al. Anxiety in Parkinson's disease: Symptom dimensions and overlap with depression and autonomic failure. Parkinsonism Relat Disord 2015; 21: 189–193. [PubMed: 25557888]

[26]. De Pablo-Fernandez E, Tur C, Revesz T, et al. Association of Autonomic Dysfunction With Disease Progression and Survival in Parkinson Disease. JAMA Neurol 2017; 74: 970–976. [PubMed: 28655059]

[27]. Medsger TA, Bombardieri S, Czirjak L, et al. Assessment of disease severity and prognosis. Clinical and Experimental Rheumatology. Epub ahead of print 2003 DOI: 10.1177/0266242613495748.

[28]. Antoniou AJ, Raja S, El-Khouli R, et al. Comprehensive Radionuclide Esophagogastrointestinal Transit Study: Methodology, Reference Values, and Initial Clinical Experience. J Nucl Med 2015; 56: 721–727. [PubMed: 25766893]

[29]. Furness JB, Callaghan BP, Rivera LR, et al. The Enteric Nervous System and Gastrointestinal Innervation: Integrated Local and Central Control. In: Advances in experimental medicine and biology, pp. 39–71.

[30]. Sletten DM, Suarez GA, Low PA, et al. COMPASS 31: A Refined and Abbreviated Composite Autonomic Symptom Score. Mayo Clin Proc 2012; 87: 1196–1201. [PubMed: 23218087]

[31]. Khanna D, Hays RD, Maranian P, et al. Reliability and validity of the University of California, Los Angeles Scleroderma Clinical Trial Consortium Gastrointestinal Tract Instrument. Arthritis Rheum 2009; 61: 1257–63. [PubMed: 19714600]

[32]. Khanna D, Nagaraja V, Gladue H, et al. Measuring response in the gastrointestinal tract in systemic sclerosis. Curr Opin Rheumatol 2013; 25: 700–6. [PubMed: 24047604]

[33]. Zilliox L, Peltier AC, Wren PA, et al. Assessing autonomic dysfunction in early diabetic neuropathy: the Survey of Autonomic Symptoms. Neurology 2011; 76: 1099–105. [PubMed: 21422460]

[34]. Leavens A, Patten SB, Hudson M, et al. Influence of somatic symptoms on PHQ-9 depression scores among patients with systemic sclerosis compared to a healthy general population sample. Arthritis Care Res (Hoboken) 2012; 64: n/a-n/a.

[35]. Chen JJ, Marsh L. Anxiety in Parkinson's disease: identification and management. Ther Adv Neurol Disord 2014; 7: 52–9. [PubMed: 24409202]

[36]. Koychev I, Okai D. Cognitive-behavioural therapy for non-motor symptoms of Parkinson's disease: a clinical review. DOI: 10.1136/eb-2016-102574.

[37]. Pellissier S, Dantzer C, Canini F, et al. Psychological adjustment and autonomic disturbances in inflammatory bowel diseases and irritable bowel syndrome. Psychoneuroendocrinology 2010; 35: 653–662. [PubMed: 19910123]

[38]. Peyrot M, McMurry JF, Kruger DF. A Biopsychosocial Model of Glycemic Control in Diabetes: Stress, Coping and Regimen Adherence. J Health Soc Behav 1999; 40: 141. [PubMed: 10467761]

[39]. Zamani-Alavijeh F, Araban M, Koohestani HR, et al. The effectiveness of stress management training on blood glucose control in patients with type 2 diabetes. Diabetol Metab Syndr 2018; 10: 39. [PubMed: 29760788]

[40]. Hanke K, Brückner CS, Dähnrich C, et al. Antibodies against PM/Scl-75 and PM/Scl-100 are independent markers for different subsets of systemic sclerosis patients. Arthritis Res Ther 2009; 11: R22. [PubMed: 19220911]

Table 1.

Demographic and clinical variables of included participants with SSc (n=46), stratified by high versus low levels of emotional well-being (UCLA SCTC GIT 2.0 well-being subscale ≥0.50). IQR= interquartile range, SSRI/SNRI= selective serotonin reuptake inhibitor/serotonin norepinephrine reuptake inhibitors, TCA= tricyclic antidepressant, RP= Raynaud's phenomenon, GI= gastrointestinal.

	Low Emotional Distress [GIT Emotional Well-Being <0.50], (n=18)	High Emotional Distress [GIT Emotional Well-Being >0.50], (n=28)	p-value
Age, median (IQR)	55 (47, 61)	58 (52, 68)	0.07
Age at Symptom Onset, median (IQR)	48 (38, 52)	46 (32, 54)	0.94
Disease Duration	8.1 (5.4, 12.0)	13.0 (6.9, 22.4)	0.09
Sex (n, % female)	15 (83)	23 (82)	0.92
Race (n, % White)	4 (22)	4 (14)	0.49
Smoking Status (% yes)			
Never	9 (50)	18 (64)	0.61
Former/Current	9 (50)	10 (36)	
Limited Skin Type (n, %yes)	10 (56)	22 (81)	0.06
Current Medications (n, % yes)			
Prednisone	1 (6)	2 (7)	0.85
Opioids	1 (6)	3 (11)	0.56
Reflux Med *	14 (78)	27 (96)	0.05
Methotrexate	1 (6)	3 (11)	0.54
Mycophenolate	5 (28)	7 (25)	0.83
SSRI/SNRI	4 (22)	10 (36)	0.33
TCA	1 (6)	1 (4)	0.75
Sleep-Aid	4 (22)	4 (14)	0.49
Benzodiazepine	3 (17)	6 (21)	0.69
Beta-Blocker	3 (17)	6 (21)	0.69
Medsger Severity Score (n, % yes)			
RP (>2)	7 (39)	8 (29)	0.47
Lung (>2)	10 (56)	13 (46)	0.55
Heart (>1)	8 (44)	11 (39)	0.73
GI (>2)	9 (50)	19 (68)	0.23
Transit: Delayed Emptying			
Esophageal	8 (47)	13 (62)	0.36
Gastric (Solid)	3 (18)	3 (13)	0.69
Small Bowel	2 (12)	2 (9)	0.75
Large Bowel	9 (53)	15 (68)	0.33
Arthralgias (%Yes)	6 (33)	15 (54)	0.15
Synovitis (%Yes)	0 (0)	3 (11)	0.15
Sicca (%Yes)	10 (56)	16 (57)	0.92
Antibody Positivity (n, %yes)			

	Low Emotional Distress [GIT Emotional Well-Being <0.50], (n=18)	High Emotional Distress [GIT Emotional Well-Being >0.50], (n=28)	p-value
Scl-70	6 (33)	6 (21)	0.37
Ro52	5 (28)	6 (21)	0.62
Centromere (A/B)	6 (33)	18 (64)	**0.04**
RNA pol-III	3 (17)	1 (4)	0.12
PM-Scl (75/100)	6 (33)	2 (7)	**0.02**

* Reflux medication defined as use of an antacid, proton pump inhibitor, or H2-blocker.

Table 2.

Symptoms of Dysautonomia according to the COMPASS-31 and SAS instruments stratified by high versus low levels of well-being (GIT 2.0 well-being subscale ≥0.50).

COMPASS-31 Mean (SD)	**Low Emotional Distress (GIT Emotional Well-Being <0.50), n=18**	**High Emotional Distress (GIT Emotional Well-Being >0.50), n=28**	**p-value**
Total	32.1 (15.6)	39.6 (18.1)	0.17
Gastrointestinal	9.6 (2.7)	14.2 (4.3)	**<0.001**
Orthostasis	10.1 (10.6)	13.3 (11.5)	0.36
Pupillomotor	2.1 (1.4)	1.9 (1.4)	0.66
Vasomotor	2.8 (1.3)	3.1 (1.3)	0.47
Bladder	1.4 (1.4)	0.9 (1.5)	0.21
Secretomotor	6.1 (3.7)	7.7 (3.6)	0.54

SAS Mean (SD)	**Low Emotional Distress (GIT Emotional Well-Being <0.50), n=14**	**High Emotional Distress (GIT Emotional Well-Being ≥0.50), n=20**	**p-value**
Column A [mean (SD)]	5.3 (1.8)	6.0 (1.8)	0.19
Column B	15.9 (5.9)	21.7 (9.0)	0.062
Gastrointestinal	3.1 (2.3)	6.9 (3.5)	**0.001**
Orthostasis	1.7 (1.1)	1.8 (1.4)	0.97
Sexual Dysfunction	4.5 (0.7)	1.7 (2.1)	0.17
Vasomotor	4.3 (3.5)	5.8 (2.6)	0.18
Bladder	1.5 (1.6)	1.5 (1.5)	0.96
Secretomotor (sudomotor)	4.7 (2.1)	5.3 (4.5)	0.70

Table 3.

Pearson correlation matrix of GIT Domains in SSc patients with moderate GI dysfunction (n=46).

	GIT Reflux	GIT Diarrhea	GIT Distension	GIT Constipation	GIT Soilage	GIT Emotional
GIT Reflux	1.00					
GIT Diarrhea	0.042	1.00				
GIT Distension	0.67	0.41	1.00			
GIT Constipation	0.25	−0.01	0.37	1.00		
GIT Soilage	0.15	0.25	0.15	−0.06	1.00	
GIT Emotional	0.30	0.37	0.49	0.25	0.33	1.00

Table 4.

Univariate and logistic regression model for emotional distress (GIT emotional well-being ≥0.50).

Independent Predictors of Emotional Distress	Univariate Model OR	p-value	Adjusted Model OR	p-value
Age	1.06	**0.049**	1.08	0.142
Disease duration	1.06	0.091	1.06	0.369
Limited Skin Type	0.60	0.11	0.41	0.155
CENP (A/B) Antibody +	3.60	**0.044**	3.30	0.306
PM-Scl (75/100) Antibody +	0.15	**0.035**	0.03	**0.031**
GI Dysautonomia (COMPASS)	1.41	**0.003**	1.85	**0.003**