THE INTERPLAY BETWEEN GASTROINTESTINAL SYMPTOMS AND NUTRITIONAL STATUS IN SYSTEMIC SCLEROSIS PATIENTS

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THE INTERPLAY BETWEEN GASTROINTESTINAL SYMPTOMS AND NUTRITIONAL STATUS IN SYSTEMIC SCLEROSIS PATIENTS (Abstract): Systemic sclerosis (SSc) is a chronic autoimmune disease frequently associated with gastrointestinal (GIT) involvement and malnutrition, which can worsen disease outcomes and quality of life. This study **aimed** to assess digestive involvement and the prevalence of malnutrition in a group of SSc patients and to evaluate the relationship between malnutrition, symptom burden, and disease activity. **Materials and methods:** We included 65 patients with SSc. The UCLA GIT 2.0 questionnaire measured the digestive symptom burden. Malnutrition risk was assessed using the Malnutrition Universal Screening Tool (MUST) and Mini Nutritional Assessment (MNA) scores. We analyzed correlations between malnutrition status, disease activity (EUSTAR-AI index), and digestive symptom burden measured by UCLA GIT 2.0 score. **Results:** Almost 70% of the subjects showed digestive involvement. The prevalence of malnutrition (MNA) was 6.6%, and the risk of malnutrition was 7.7% (MUST). Malnourished individuals experienced significantly higher scores in UCLA (p=0.009), UCLA reflux (p=0.05), UCLA emotional well-being (p=0.001), and UCLA social function (p=0.08), as well as increased disease activity scores (EUSTAR-AI—p=0.027). **Conclusions:** Digestive involvement and malnutrition are frequent among SSc patients, particularly those with higher disease activity scores and GIT involvement. These results highlight the need for rapid gastrointestinal and nutritional management in SSc to improve patient outcomes and quality of life. **Keywords:** SYSTEMIC SCLEROSIS, GASTROINTESTINAL, MALNUTRITION.

INTRODUCTION

Systemic sclerosis (SSc) is a systemic autoimmune disease, with a complex pathogenesis, characterized by skin fibrosis, vasculopathy and internal organs malfunction. The most common symptoms are Raynaud's phenomenon and skin fibrosis (1,2). There are two main subsets of the disease (the limited cutaneous form – lcSSc and the diffuse cutaneous form – dcSSc) that have different developments but also share many characteristics (3). DcSSc is characterized by an early and accelerated organ involvement, a severe prognosis and the presence of anti-Scl 70 antibodies (also known as anti topoisomerase1 antibodies). LcSSc is expressed by a gradual disease development, later

visceral involvement, anti-centromere antibodies positivity, and a better disease prognosis (1,4,5).

After skin, the gastrointestinal tract (GIT) is the second most frequently affected organ. Digestive involvement is observed in 90% of the patients, secondary to progressive fibrosis of the GIT, spanning from the oral cavity to the anus (2,6). This determines the dysmotility and hypomotility of the esophagus, the small intestine, and the gut (7). The GIT involvement causes serious morbidity and affects the survival of these patients (8). The digestive manifestations of SSc may vary depending on the affected area of the GIT (8,9,10). Esophageal symptoms are reported by up to 90% of patients (4). In general, patients experience mild gastroesophageal reflux disease. However, severe dysmotility of the upper and/or lower bowel can also be present in some cases, causing severe manifestations. For example, almost half of the patients experience gastric dysfunction characterized mainly by gastroparesis and gastric antral vascular ectasia (GAVE) (2,11). Dysmotility of the small bowel occurs in up to 80% of the subjects, with the small intestine being considered the second most affected digestive organ (2,12). As far as the colon is concerned, in up to 50% of the patients varying bowel patterns may be observed, alternately constipation and diarrhea or other symptoms such as bloating, distention, malnutrition or bleeding (13,14).

The GIT can be involved in both forms of SSc, although it can be more frequent or more severe in the diffuse phenotype. Other risk factors for severe GIT involvement include male sex, myopathy, and sicca symptoms (15). The severity of digestive symptoms is also associated with emotional distress and depressive disorders (16,17).

It is not entirely understood how the SSc-GIT symptoms develop over time and despite the significant prevalence of GIT disease in SSc, there are few available treatments (18). Severe digestive involvement can lead in time to malnutrition.

In SSc, malnutrition is reported as an independent risk factor for mortality, being associated with cardiac and gastrointestinal involvement, inflammatory status, dysphagia, and chronic intestinal pseudo obstruction (19,20). Malnutrition results from GIT involvement but also intensifies the illness, creating a vicious cycle of deteriorating nutritional status and exacerbating systemic symptoms.

Depending on the assessing methods used for defining the risk of malnutrition, its prevalence in SSc ranges between 18% and 38% (21,20). For example, when using the MUST score, in a Canadian cohort of 586 SSc patients, 10.8% were at medium risk for malnutrition and 17.4% were at high risk. When compared to MUST score for hospitalized patients, the results were similar (21). Higher prevalence of malnutrition were obtained by a French study group that defined malnutrition as one of the following three options: weight loss of > 5% over one month or more than 10% over 6 months, BMI < 21 kg/m^2, or albuminemia < 35 g/L. In their cohort, 38.3% were at high risk according to MUST, 59.2% of the patients were diagnosed with malnutrition, and 25% had severe malnutrition (20).

There are various screening tools for malnutrition and the ESPEN recommends using Nutritional Risk Screening 2002 (NRS – 2002) for patients in the hospital, MUST (The Malnutrition Universal Screening Tool) in the community, and the first part of MNA (Mini Nutritional Assessment) for elders (22).

To assess the digestive involvement in SSc, clinicians can use the University of California at Los Angeles Scleroderma Clin-

ical Trial Consortium GIT 2.0 (UCLA SCTC GIT 2.0) instrument. Although objective studies are the gold standard for diagnosis of GIT involvement, UCLA SCTC GIT 2.0 reflux and distention/bloating scales are sensitive enough and complement the objective methods (23). It is a validated questionnaire, completed by the patient that evaluates seven domains covering a variety of digestive symptoms. It can also highlight the need for further investigations of the GIT, being a useful tool in the screening of SSc patients (24).

It can be very difficult to identify individuals who are at a high risk of experiencing clinically substantial weight loss or malnutrition because GIT symptoms are frequent in SSc patients. In this context, we aimed to explore the range of gastrointestinal symptoms in patients with SSc and evaluate if there are any correlations with the risk of malnutrition.

MATERIALS AND METHODS

We performed an observational study in which we included 65 patients with a SSc diagnosis according to the American College of Rheumatology/European League Against Rheumatism (EULAR) 2013 classification criteria for SSc. The patients were adults admitted to the rheumatology department for revaluation. Patients with mixed connective tissue disease, overlap syndrome, neoplasia, or who refused to participate were excluded.

Information about age, sex, use of immune modulatory treatment, the type of SSc according to LeRoy criteria (25), and other clinically relevant data for our study were taken from the medical records. The modified Rodnan skin score (mRSS) was used for skin involvement assessment. Using venous blood samples, we performed within the hospital laboratory a biochemical evaluation. The hospital laboratory also measured the serum antinuclear antibodies, anti-topoisomerase I, and anticentromere antibody titers. Esophageal reflux presence was considered if patients complained about heartburn or regurgitation. The disease activity was evaluated using the EUSTAR-AI tool (European Scleroderma Trials and Research group Activity Index). Active disease was defined as having an EUSTAR-AI score exceeding 2.5.

We also evaluated the following anthropometric parameters: height (H), weight (W), and body mass index (BMI, calculated as W/H^2). Using the World Health Organization definition for BMI classes our subjects were divided into underweight (BMI under 18.5 kg/m^2), eutrophic (BMI between 18.5 and 24.9 kg/m^2), pre-obesity (BMI between 25.0 and 29.9 kg/m^2) and obesity (BMI greater than 30 kg/m^2).

To evaluate the digestive involvement we used a translated, adapted, and validated version of the UCLA GIT 2.0 questionnaire (26). The questionnaire included 7 categories of symptoms: reflux, distention/bloating, fecal continence, diarrhea, constipation, social function, and emotional well-being. The final score is the average of the scores for each category (except constipation) and may vary between 0 and 2.83. We defined the presence of gastrointestinal involvement if the patients had a total score or at least one of the seven categories > 0. The score was interpreted as previously described by van Leeuwen et al. (27). It was divided into none-mild (a score of 0 or < 0.5), moderate (a score ≥ 0.5 but less than 1.01), and severe (≥ 1.01). For fecal incontinence and distention/bloating items, the symptoms were considered none-mild for a score < 1.01, moderate ≤ 1.61 for distention/bloating and ≤ 2.01 for fecal soiling, and severe if the score was > 1.61 for distention/bloating and > 2.01 for fecal soiling.

The risk of malnutrition was evaluated using the translated version of MNA (Mini Nutritional Assessment) score where malnutrition was defined with a score less than or equal to 7, risk of malnutrition with scores between 8 and 11, and normal nutrition with values greater than 11. We also performed the MUST score and patients were classified as being at low risk (MUST score = 0), at moderate risk (MUST score = 1) or at high risk of malnutrition (MUST score ≥ 2).

The Ethics Research Committee of the Clinical Rehabilitation Hospital from Iasi and the University of Medicine and Pharmacy "Grigore T. Popa" Iasi approved the study and ensured compliance with the principles of the Declaration of Helsinki. Subjects gave written informed consent to undergo the examination.

For the statistical analysis, the tests were performed on SPSS version 26. Categorical variables were presented as proportions and Fisher's test was performed. Continuous variables were expressed as mean and standard deviation. Statistically significant differences between patients with lcSSc and dcSSc were assessed by independent *t* test.

RESULTS

General characteristics. A number of 65 patients with SSc met the inclusion criteria and completed the questionnaires. According to the LeRoy classification criteria, 27 had a limited form of SSc, and 38 had a diffuse subset. The majority were women (86.2%) with a mean age of 57.15 (±10.35) years old. The mean disease duration was 8.48 (±7.09) years. Anticentromere antibodies were present in 38.5% of the patients, while 49.2% of the subjects were positive for anti-SCL70 antibodies.

The demographic and other clinical data are displayed in the first table. The results are expressed as mean ± standard deviation for continuous variables and as number (percentage) for categorical variables. Inflammatory syndrome was considered if either ESR or CRP were elevated. mRSS – modified Rodnan skin score; BMI – body mass index; ILD – interstitial lung disease.

Inflammatory syndrome, described as the presence of ESR (erythrocyte sedimentation rate) and CRP (C reactive protein) above the laboratory normal values, was identified in 52.3% of the patients, more than half of whom had dcSSc.

Interstitial lung disease (ILD) was reported in 63.1% of the patients, mainly in dcSSc subjects (73.7%, *p=0.04)*. Patients with ILD had more often SCL70 antibodies (*p= 0.01)*, higher mRSS skin scores (*p=0.002),* and higher values for muscular enzymes (creatine kinase – *p=0.04* and lactate dehydrogenase – *p=0.014*).

Digestive involvement

Digestive involvement was considered in patients who exhibited gastrointestinal tract symptoms and was present in nearly 70% of those included. Dysphagia was reported in 53.8% of the patients, slightly more frequent in the dcSSc type (55% vs 51%). Early satiety was present in 49.2% of the subjects, of which 63% had lcSSc (*p=0.08)*. Esophageal reflux was spotted in 76.9% of the subjects, with no difference between the two subsets of the SSc. Patients with reflux also had lower interincisive distance (p= 0.05), lower weight, higher CRP levels, and higher EUSTAR-AI scores– with no statistical significance.

Significant differences according to t test for continuous variables and Fisher's exact test for categorical variables comparing lcSSc to dcSSc are highlighted by p values.

The overall UCLA GIT 2.0 score was similar between the two phenotypes of SSc, with the majority of the patients describing none to mild symptoms. Patients with

dcSSc were more likely to have reflux, but the results did not reach statistical significance (0.79 vs 0.69). Furthermore, the reflux symptoms were more serious in dcSSc patients, as 13 vs 5 patients experienced severe UCLA GIT 2.0 scores. UCLA constipation score was higher in lcSSc patients compared to dcSSc patients (0.59 vs 0.36, *p=0.08*) but the difference did not reach statistical significance. Regarding the other domains of the UCLA SCTC 2.0 tool, the scores were similar between the two groups of lcSSc and dcSSc, most of the patients describing none to mild symptoms in all of the categories (tab. II).

Patients with extensive cutaneous involvement, according to mRSS score, had higher UCLA reflux scores (*p=0.07)*.

Anticentromere positivity correlated with higher scores for UCLA (*p=0.048)*, UCLA social function (*p=0.049*), UCLA emotional well-being (*p=0.036),* and UCLA constipation (*p=0.003)*. Furthermore, anticentromere antibodies correlated with moderate digestive involvement according to UCLA severity (*p=0.012)*.

TABLE I.

Characteristics of the study subjects.

General characteristics	Overall (n=65)	lcSSc (n=27)	dcSSc (n=38)	*p*
Age	57.15 ± 10.35	60.44 ± 8.11	54.82 ± 11.20	0.02
Gender, n (%female)	86.2%	100%	76.3%	0.008
Disease duration	8.48 ± 7.09	11.41 ± 7.9	6.39 ± 5.6	0.007
SCL 70 (%)	49.2%	7.7%	78.9%	0.000
Anticentromere antibodies (%)	38.5%	81.5%	8.1%	0.000
mRSS	11.77 ± 6.6	9.67 ± 4.51	13.3 ± 7.5	0.012
ILD	63.1 %	48.1%	73.7%	0.042
Inflammatory Syndrome	52.3%	40.7%	60.5%	0.1
Anemia	67.7%	66.7%	68.4%	1
Dysphagia	53.8%	51.9%	55.3%	0.8
Early satiety	49.2%	63%	39.5%	0.08
Reflux	76.9%	77.8%	76.3%	1
BMI classification				
Underweight (BMI< 18.5)	6.2%	0 %	10.5%	
Healthy weight (BMI = 18.5 – 24.9)	44.6%	51.9 %	39.5 %	
Overweight (BMI = 25 – 29.9)	36.9 %	37 %	36.8 %	
Obesity (BMI >30)	12.3%	11.1 %	13.2 %	
MNA classification				
Normal	43.1 %	41.7 %	58.1 %	
At risk	35.4 %	50 %	35.5 %	
Malnourished	6.2 %	8.3 %	6.5 %	
MUST classification				
Low risk	66.2 %	75 %	80.6 %	
Moderate risk	10.8 %	20.8 %	6.5 %	
High risk	7.7 %	4.2 %	12.9 %	
EUSTAR – AI	1.91 ± 1.25	1.55 ± 1.08	2.17 ± 1.31	0.051
Active disease (≥ 2.5)	27.7 %	14.8 %	37.8 %	0.053
Inactive disease (< 2.5)	70.8 %	85.2 %	62. 2%	

TABLE II.

Results of the UCLA SCTC 2.0 questionnaire

UCLA SCTC 2.0	Overall (n=65)	lcSSc (n=27)	dcSSc (n=38)	*p*
UCLA score	0.43 (0.387)	0.461 (0.41)	0.408 (0.374)	
None-Mild, n (% total)	44 (67.7%)	17 (63%)	27 (71.1%)	
Moderate, n (% total)	15 (23.1 %)	8 (29.6 %)	7 (18.4 %)	
Severe, n (% total)	6 (9.2 %)	2 (7.4 %)	4 (10.5 %)	
UCLA Reflux	0.752 (0.607)	0.69 (0.513)	0.796 (0.669)	
None-Mild, n (%total)	25 (38.5%)	9 (33.3%)	16 (42.1 %)	
Moderate, n(%total)	22 (33.8 %)	13 (48.1 %)	9 (23.7 %)	
Severe, n (% total)	18 (27.7 %)	5 (18.5 %)	13 (34.2 %)	
UCLA Distention	0.788 (0.856)	0.935 (0.916)	0.684 (0.806)	
None-Mild n (%total)	47 (72.3%)	19 (70.4%)	28 (73.7%)	
Moderate, n(%total)	8 (12.3 %)	3 (11.1 %)	5 (13.2%)	
Severe, n (% total)	10 (15.4 %)	5 (18.5%)	5 (13.2%)	
UCLA Fecal soilage	0.123 (0.545)	0.185 (0.622)	0.078 (0.486)	
None-Mild n (%total)	63 (96.9%)	26 (96.3%)	37 (97.4%)	
Moderate, n(%total)	0 (0%)	0 (0%)	0 (0%)	
Severe, n (% total)	2 (3.1%)	1 (3.7%)	1 (2.6%)	
UCLA Diarrhea	0.130 (0.333)	0.074 (0.266)	0.171 (0.372)	0.052
None-Mild n (%total)	54 (83.1%)	25 (92.6%)	29 (76.3 %)	
Moderate, n(%total)	9 (13.8%)	2 (7.4%)	7 (18.4 %)	0.071
Severe, n (% total)	2 (3.1%)	0 (0 %)	2 (5.3 %)	
UCLA Social function	0.254 (0.342)	0. 325 (0.389)	0.205 (0.3)	
None-Mild n (%total)	49 (75.4%)	19 (70.4 %)	30 (78.9%)	
Moderate, n(%total)	13 (20%)	6 (22.2 %)	7 (18.4 %)	
Severe, n (% total)	3 (4.6 %)	2 (7.4%)	1 (2.6%)	
UCLA Emotional well-being	0.53 (0.638)	0.556 (0.631)	0.512 (0.651)	
None-Mild n (%total)	36 (55.4%)	14 (51.9%)	22 (57.9%)	
Moderate, n(%total)	18 (27.7%)	10 (37%)	8 (21.1 %)	
Severe, n (% total)	11 (16.9%)	3 (11.1%)	8 (21.1%)	
UCLA constipation	0.457 (0.535)	0.592 (0.524)	0.361 (0.528)	0.08
None-Mild n (%total)	34 (52.3%)	11 (40.7 %)	23 (60.5 %)	
Moderate, n(%total)	24 (36.9 %)	11 (40.7 %)	13 (34.2 %)	0.054
Severe, n (% total)	7 (10.8 %)	5 (18.5 %)	2 (5.3 %)	

Malnutrition. According to MUST, the risk of malnutrition was high in 7.7% of the patients, moderate in 10.8%, and low in 66.2%. Subjects with a high risk had lower interincisive distance (p=0.03) and higher scores in almost all of the UCLA domains except constipation, but the results did not reach statistical significance.

Based on the MNA, malnourished individuals (6.2% of the subjects) experienced higher values for UCLA (*p= 0.009)*, UCLA reflux (*p=0.05)*, UCLA emotional well-being (*p= 0.001)*, and UCLA social function (*p=0.08)*. Malnourished patients also had higher disease activity scores calculated with the EUSTAR-AI index (*p= 0.027)*. MNA evaluation score also correlated with the presence of dysphagia (*p=0.05)*.

DISCUSSION

In current literature, GIT involvement is present in nearly all SSc patients at various

extents (28). According to the 2012 EUSTAR cohort, gastroesophageal symptoms are the most common, reported in more than 60% of the patients (29). GERD symptoms are more frequently reported (in almost 80% of the cases) if ILD is associated (30). In very early SSc, severe GIT involvement can be present in 15% of the cases, being associated with telangiectasias, higher skin scores, inflammatory myositis, but also with high mortality and low quality of life (31). Severe gastrointestinal involvement can initially lead to unintentional weight loss, which may become significant and result in malnutrition. Male sex, dcSSc, digital ulcers, shorter disease duration, elevated erythrocyte sedimentation rate (ESR)/C-reactive protein, elevated creatine kinase (CK), pulmonary hypertension, aberrant diastolic dysfunction, and interstitial lung disease were among the clinical characteristics linked to significant weight loss (32).

Using the UCLA SCTC GIT 2.0 tool, the severity of the GIT symptoms varies from absent to very mild in 39% of the patients, to mild in 21% of the patients, moderate in 31%, and severe to very severe in 9% of the patients (24). A more recent study that included 834 SSc patients, which used the UCLA SCTC GIT 2.0 questionnaire to evaluate the digestive symptoms, reported none to mild in 73% of the subjects, moderate in 21%, and severe in 7% of the subjects. The same study declared that female sex, smoker status, presence of anticentromere antibodies, and corticosteroid usage were associated with more severe GIT involvement (27).

In the present study, we report that nearly 70% of the patients with SSc experience digestive symptoms, especially gastroesophageal reflux. Alastal *et al*. reported a frequency of 59.24 % for digestive involvement, and GERD was present in 34.8% of the subjects included (33).

The severity of digestive symptoms correlated with the presence of anticentromere antibodies, as these patients reported higher scores for nearly all UCLA domains. These results align with those previously described in the literature (27).

MUST and MNA scores focus slightly differently depending on the questions included: MUST focus more on BMI, recent weight loss, and acute disease, while MNA includes questions on dietary intake, mobility, and psychological stress. According to MNA, 6.2% of the patients in our study group were malnourished. Cano Garcia *et al*. reported lower malnutrition rates using the same index and correlated the results with diffuse skin involvement and sarcopenia (34). According to MUST, 7.7 % of our study group were at high risk of becoming malnourished. We obtained lower rates of malnutrition in our study compared to the existing literature (20,21).

Malnutrition exacerbates GIT symptoms, resulting in a vicious cycle of worsening systemic symptoms and declining nutritional status. Caimmi *et al*. (35) have previously demonstrated that MUST scores correlate with UCLA GIT values. In our case, we obtained higher UCLA scores in malnourished patients, suggesting that digestive involvement impacts their food intake, emotional well-being, and social functioning.

Furthermore, we observed a connection between malnutrition and disease severity measured with the EUSTAR-AI index. A more active disease often involves systemic inflammation, which can increase metabolic demands and reduce nutrient absorption. In our study group, malnutrition seems to be both a consequence of high disease burden and GIT involvement but also a factor that may intensify symptom severity.

The current investigation is constrained by a limited sample size of enrolled pa-

tients. Another limitation is that UCLA GIT is a self-reported questionnaire designed to assess symptoms in the past seven days, potentially introducing bias. Patients with GIT symptoms were not further evaluated with objective measurements to confirm the digestive pathology.

CONCLUSIONS

In conclusion, our data gives information about the high frequency of GIT symptoms in patients with SSc. The assessment of digestive involvement using the UCLA SCTC GIT 2.0 questionnaire provides a systematic approach to characterize the spectrum of GIT manifestations. It facilitates early detection of GIT symptoms and their impact on patient's quality of life, enabling clinicians to further recommend objective methods for the diagnosis of GI disease. Digestive involvement in systemic sclerosis patients often leads to nutritional impairment. Malnutrition can worsen the severity of SSc, creating a cycle where increased disease activity and symptom burden further deteriorate nutritional status.

CONFLICT OF INTEREST AND FUNDING

The authors declare that there is no conflict of interest, and they received no specific funding.

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