The assessment of malnutrition and severity of gastrointestinal disease using symptom-based questionnaires in systemic sclerosis: is it related to severe organ involvement or capillary rarefaction at microcirculation?

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ABSTRACT

Objective. *Gastrointestinal (GI) system is commonly affected in sytemic sclerosis (SSc) patients who are also known to be at risk for malnutrition. We aimed to investigate the relationship between severity of GI disease, malnutrition and severity of organ involvement including microvasculopathy.*

Methods. *One hundred and thirty-four SSc patients were included into the study; disease activity and severity, the University of California, Los Angeles, Scleroderma Clinical Trials Consortium Scleroderma Gastrointestinal scale 2.0 (UCLA SCTC GIT 2.0) and malnutrition universal screening tool (MUST) were cross-sectionally assessed. Nailfold video-capillaroscopy (NVC) was performed to evaluate microvasculopathy.*

Results. *SSc patients who are at medium to high risk for malnutrition (n=20); had more frequently limited pulmonary function, lung involvement, pulmonary hypertension, capillary rarefaction and NVC late pattern than those at low risk for malnutrition. Capillary rarefaction (≤6/mm) was shown to be independently associated with medium to high risk for malnutrition defined by using MUST. Capillary rarefaction and severe skin involvement were found to be independently related to* 'severe' *or* 'very severe' GI disease *defined by using UCLA SCTC GIT 2.0. UCLA SCTC GIT 2.0 scores were not found to be good discriminative in patients at risk for malnutrition allowing for a ROC curve of area under the curve (AUC)<0.8).*

Conclusion. *Assessment of gastrointestinal complaints and nutritional status by using symptom based questionnaires reflected the severity of GI disease and malnutrition including some limitations. Capillary rarefaction and severe skin involvement might be determining factors for malnutrition risk and severe GI disease.*

Introduction

Gastrointestinal (GI) system is commonly affected in sytemic sclerosis (SSc) and is reported in 71% at early course and up to 90% during disease duration (1, 2). GI disease is one of the substantial causes of morbidity and mortality in SSc (3, 4). The University of California, Los Angeles, Scleroderma Clinical Trials Consortium Scleroderma Gastrointestinal scale 2.0 (UCLA SCTC GIT 2.0) is a validated tool to assess GI disease and its impact on patient's well-being in SSc (5-10). Of the GI scales, 'reflux' and 'distension' items were shown to have a good sensivity for the assessment of upper GI (11).

SSc patients with GI disease were also known to be at risk for malnutrition due to probable causes of dysmotility, malabsorption, nausea and vomiting. Besides GI disease; impaired functional status due to digital ulcers, hand disease, low lung capacity, fatigue and myalgia/myositis, oropharyngeal involvement such as reduced saliva and impaired oral aperture, mood disorders were the other causes accused for malnutrition (12). Malnutrition was reported as 18% in a large Canadian SSc cohort consisting of 586 patients (13), nonetheless reported frequencies in the literature were found to be ranged depending on the definition used (14).

Nailfold video-capillaroscopy (NVC) was widely accepted as a complementary tool for diagnosis, therefore NVC abnormalities were included into ACR/EULAR classification criteria for SSc (15). It has been shown to be useful to

predict the severity of heart, peripheral vascular and pulmonary involvements in SSc (16-18). We aimed to investigate the relationship between severity of GI disease and risk for malnutrition evaluated by patient reported questionnaires and severity of organ involvement.

Methods

Study design and patients

A total of 134 consecutive SSc patients fulfilling ACR/EULAR classification criteria (14) were included into the study and cross-sectionally assessed. All patients signed informed consent to be a participant. Demographics, cumulative organ involvement, treatment and laboratory including current acute phase response (ESR>20 mm/ hour and/or CRP >5 mg/L were accepted as high acute phase response), echocardiography, high-resolution computed tomography (HRCT) of chest and respiratory function tests within 6 months prior to visit were recorded into a predefined protocol. Current modified Rodnan skin score (MRSS), disease activity score (19) (different scores of 10 parameters, the total possible activity score was 10) and organ severity scores (20) (score of 0 to 4 for 9 involvements) were calculated.

Assessment of severity of GI disease and malnutrition

UCLA SCTC GIT 2.0 and malnutrition universal screening tool (MUST) were evaluated in all participants. The original version of the questionnaire forms were filled by the same physcian (YY). UCLA SCTC GIT 2.0; 7 multi-item areas (reflux, distension, soilage, diarrhea, social functioning, emotional well-being and constipation) including total of 34 items scored from 0 to 3 (lower indicates better). Total score averages 6 areas excluding constipation and scored 0 (no GI symptom) to 3 (most severe) (5). To report the nutrition status of the patients, 'malnutrition universal screening tool (MUST)' was calculated by the sum of scores of body mass index (BMI), weight loss in past 3-6 months and no nutritional intake currently affected by acute disease. Overall risk for malnutrition was defined as follows; low risk if MUST score=0, medium risk if MUST score=1 and high risk if MUST score ≥2 (21).

Assessment of the microvasculature: nailfold video-capillaroscopy (NVC)

NVC was performed after 20 minutes resting in a room with constant temperature of 20–22°C by a video-capillaroscopy (Dino-Lite, digital microscope). Two representative images for each of second to fifth fingers of right and left hands (16 images for 8 fingers) were captured with x200 optical probe after a drop of cedar oil on the nailfold and stored by Dinocapture 2.0 programme to determine the scleroderma patterns. All stored images were analysed by the first author later.

Scleroderma patterns were classified qualitatively as follows (22): 'early' NVC pattern, regular capillary distribution, no significant loss of capillaries (at least 9 capillaries at per linear mm counted at the distal row of nailfold), few giant capillaries (homogeneously enlarged capillary loop with a diameter of 50 μm) and few capillary haemorrhages (dark aggregates due to haemosiderin deposits), 'active' NVC pattern, frequent giant capillaries and haemorrhages, moderate loss of capillaries, absent or mild ramified capillaries (branching or bushy capillaries often originating from a single capillary) and mild disorganisation of capillary architecture (irregular capillary distribution, heterogenously shaped capillary loops), 'late' NVC pattern, irregularly enlarged capillaries, few/absent giant capillaries and capillary haemorrhages, severe loss of capillaries with avascular areas, frequent ramified capillaries and disorganisaiton of normal capillary architecture. In addition, NVC was evaluted semi-quantitatively; capillary density was calculated as the average of number of capillaries per linear mm counted at the distal row of nailfold for 8 digits.

Statistical analysis

Statistical analyses were performed by using SPSS 17.0 (SPSS Inc. Chicago, IL). Patient characteristics and capillaroscopic patterns were summarised by using descriptive statistics. Continuous variables were reported as mean (±standard deviation=SD) and categorical variables as percentages.

The comparisons of clinical characteristics and NVC patterns between patients grouped according to risk for malnutrition status and BMI were made by chi-square test; disease assessment paramaters, scores of UCLA SCTC GIT 2.0 and capillary density were analysed by using Mann-Whitney U-test. Receiver operating characteristics (ROC) analysis was performed to determine the relationship between UCLA SCTC GIT 2.0 scores and risk for malnutrition according to MUST score. Area under the curve (AUC) was calculated.

Clinical parameters and capillaroscopic abnormalties were calculated by using logistic regression analysis with presence of medium to high risk for malnutrition or severe UCLA SCTC GIT 2.0 score as dependent variables. Severity of GI disease was determined according to 2 different cut-off values; first, UCLA SCTC GIT 2.0 score higher than median level of 0.1660 was accepted as 'severe GI involvement'and second, higher than 0.7325 according to ROC analysis was accepted as 'very severe GI involvement'. Univariate and multivariate analysis appliying forward stepwise were performed for disease duration (<5 years), all severe organ involvements according to Medsger severity index and NVC scleroderma patterns. *p*-values <0.05 were considered as significant.

Results

The total number of patients analysed were 134 (124 females, 92.5%). The mean age was 50.2±12.3 years (range: 18–73 years) and duration of follow-up was 47.8±56.7 months (range: 0.5-240 months). The mean duration of Raynaud's and non-Raynaud's symptoms (years) were 9.6±8.9 (range: 0.5–50) and 6.2±6.4 (range: 0.5–44) years.

Of the patients, 114 (85%) were found to be at low risk (MUST score=0), 12 (9%) were at medium risk (MUST=1) and 8 (6%) were at high risk (MUST≥2) for malnutrition. Five of the patients (0.036% of total) who were at risk for malnutrition required enteral nutrition. Frequency of risk for malnutrition was found to be similar at early and late disease (duration of non-Raynaud's symptom ≤5 *vs*. >5 years) in SSc patients

Table I. The prevalence of characteristics in SSc patients.

		All patients n. (%)	MUST = 1 to 4 n. (%)	MUST = 0 n. (%)	*p*
Cutaneous subset	Diffuse cutaneous SSc	33 (24.6)	6 (30.0)	27 (23.7)	NS
	Limited cutaneous SSc	90 (67.2)	13 (65)	77 (67.5)	NS
	Asclerodermic SSc	11 (8.2)	1 (5.0)	10 (8.8)	NS
Autoantibodies	ANA	122 (89.1)	15 (75.0)	104 (91.2)	0.010
	Anti-centromere	34 (24.8)	1 (5.0)	33 (28.9)	0.023
	Anti-Scl70	37 (28.4)	5 (25.0)	32 (28.1)	NS
Clinical manifestations	Raynaud's	129 (96.3)	20 (100)	109 (95.6)	NS
	Digital ulcers	60 (44.8)	13 (65)	47 (41.2)	NS
	Synovitis	34 (25.4)	8 (40)	27 (22.8)	NS
	Flexion contractures	18 (13.4)	4 (20)	14 (12.3)	NS
	Tendon friction rubs	8 (6.0)	2 (10)	6 (5.3)	NS
	Renal crisis	1 (0.7)	0 (0)	1 (0.9)	NS
	Arrhythmia	3 (2.2)	1 (5.0)	2 (1.8)	NS
	FVC <80%	35 (26.1)	10 (50)	25 (21.9)	0.011
	DLCO <80%	59 (44.0)	13 (65)	46 (40.4)	0.044
	Interstitial lung disease	50 (37.3)	12 (60.0)	38 (33.3)	0.024
	PH (n=13, PAH by RHC)	20 (14.9)	5 (25)	15 (13.2)	NS
Treatment	Immunosuppressives	67 (50.0)	12 (60)	55 (48.2)	NS
	Steroids	64 (47.7)	12 (60)	51 (44.8)	NS
	Specific vasodilator agents	34 (25.4)	6 (30)	28 (24.6)	NS

ANA: anti-nuclear antibody; PH: pulmonary hypertension; PAH: pulmonary arterial hypertension; RHC: right heart catheterisation.

Table II. Disease assessment parameters, UCLA SCTC GIT 2.0 scores and NVC scleroderma pattern in SSc patients.

	All patients (n=134)	MUST score = 1-4 (n=20)	MUST score = 0 (n=114)	*p*
Modified Rodnan skin score	7.19 ± 6.55	9.40 ± 8.05	6.81 ± 6.22	NS
Disease activity score	1.80 ± 4.93	4.35 ± 11.99	1.32 ± 1.27	NS
Disease severity score	5.30 ± 3.60	6.00 ± 3.24	5.18 ± 3.66	NS
UCLA SCTC GIT 2.0-total	0.24 ± 0.27	0.43 ± 0.38	0.21 ± 0.24	*p*=0.015
reflux	0.65 ± 0.61	1.03 ± 0.81	0.59 ± 0.54	*p*=0.026
distension	0.31 ± 0.66	0.56 ± 0.83	0.27 ± 0.62	NS
soilage	0.10 ± 0.37	0.20 ± 0.41	0.08 ± 0.36	*p*=0.042
diarrhoea	0.23 ± 0.55	0.38 ± 0.60	0.20 ± 0.53	NS
social functioning	0.09 ± 0.24	0.29 ± 0.46	0.06 ± 0.16	*p*<0.001
emotional wellbeing	0.08 ± 0.26	0.20 ± 0.39	0.06 ± 0.23	*p*=0.012
constipation	0.14 ± 0.35	0.21 ± 0.50	0.14 ± 0.33	NS
NVC (%) normal	12 (9)	1 (5)	11 (9.6)	NS
early	27 (20.1)	1 (5)	26 (22.8)	NS
active	23 (17.2)	2 (10)	21 (18.4)	NS
late	72 (53.7)	16 (80)	56 (49.1)	*p*=0.014
Capillary number/mm	5.99 ± 2.10	4.90 ± 2.10 (4-9)	6.18 ± 2.06	*p*=0.020

(14.7% *vs*. 14.8%). The prevalence of characteristics in patient groups were summarised in Table I. SSc patients who were at medium to high risk for malnutrition (MUST ≥1) (n=20, 18 females); had more frequent limited FVC or DLCO%, lung involvement and pulmonary hypertension, less frequent ANA and anti-centromere positivity than compared to those at low risk for malnutrition (p<0.05). BMI levels were <18.5 in 5 (3.6%), 18.5–20 in 7 (5.1%), >20 in 122 (87.7%) patients. BMI alone was not found to be related to disease characteristics, disease activity and severity. MRSS, disease activity and severity scores were not significantly different, capillary number was shown to be less and NVC late pattern was frequent in patients who were at medium to high risk for malnutrition compared to those at low risk for malnutrition (Table II).

UCLA SCTC GIT 2.0 scores are summarised in Table II. The patients with early disease (duration of non-Raynaud's symptom ≤5 years) had less UCLA SCTC GIT 2.0 'total', 'reflux' and distension scores (0.21±0.27 *vs*. 0.27±0.24, p=0.031, 0.54±0.58 *vs*. 0.81±0.59, p=0.006, 0.20±0.50 *vs*. 0.46±0.80, p=0.002, respectively). UCLA SCTC GIT 2.0 'total' and 'reflux, soilage, social functioning and emotional wellbeing' scores were shown to be higher in patients who were at medium to high risk for malnutrition than compared to those at low risk for malnutrition.

Total UCLA SCTC GIT 2.0 score (≥0.7325) was found to be poorly discriminative in patients at medium to high risk for malnutrition as compared with at low risk for malnutrition allowing for a ROC curve of area under the curve AUC=0.673. UCLA SCTC GIT 2.0 - reflux score was found to be fairly discriminative (AUC=0.772) in patients who have MUST-weight loss score (≥1) (AUC <0.7).

In terms of severity of organ involvement, severe joint/tendon involvement (Medsger score of 2 to 4), severe GI disease (UCLA SCTC GIT 2.0 score ≥0.1660), NVC late pattern and capillary rarefaction (number of capillaries ≤6/mm), were shown to be related to risk for malnutrition. After multivariate analysis capillary rarefaction was the only independent factor associated with medium to high risk for malnutrition (Table III).

Severe lung and severe PVI involvement (Medsger score of 2 to 4 for both), early and late NVC patterns and capillary rarefaction were found to be related to *severe GI disease* (UCLA SCTC GIT 2.0 score ≥0.1660), while multivariate analysis showed capillary rarefaction was independently associated with severe GI *disease*. Severe skin involvement (Medsger score of 2 to 4) and capillary rarefaction were found to be related to *very severe GI disease* (UCLA SCTC GIT 2.0 score (≥0.7325), while multivariate analysis showed severe skin involvement was independently associated with very severe GI *disease* (Table III).

Discussion

Our study revealed that 15% of our SSc cohort were at medium to high risk for malnutrition and 3.6% required enteral nutrition, these patients were shown to have less pulmonary function, frequent lung involvement and pulmonary hy-

Table III. Logistic regression analysis for clinical and NVC parameters associated with risk for malnutrition and severe GI disease.

Risk for Malnutrition (MUST≥1)	Univariate analysis OR (95% CI), *p*	Multivariate analysis OR (95% CI), *p*
severe joint/tendon	3.848 (1.005-14.736), *p*=0.049	
severe GI (GIT score ≥0.1660)	3.462 (1.178-10.174), *p*=0.024	
capillary rarefaction (≤6/mm)	4.304 (1.462-12.673), *p*=0.008	
NVC late pattern	4.143 (1.305-13.157), *p*=0.049	3.818 (1.280-11.387), *p*=0.016
Severe GI (GIT score ≥0.1660)	Univariate analysis OR (95% CI), *p*	Multivariate analysis OR (95%CI), *p*
severe lung involvement	2.737 (1.166- 6.423), *p*=0.021	
severe PVI involvement	2.647 (1.260-5.562), *p*=0.010	
NVC early pattern	0.228 (0.089-0.582), *p*=0.002	
NVC late pattern	3.273 (1.603- 6.683), *p*=0.001	
capillary rarefaction (≤6/mm)	4.191 (2.004-8.765), *p*<0.001	4.242 (1.987- 9.059), *p*<0.001
Very Severe GI (GIT score ≥0.7325)	Univariate analysis OR (95% CI), *p*	Multivariate analysis OR (95%CI), *p*
severe skin involvement	5.385 (1.341- 21.623), *p*=0.018	5.282 (1.315- 21.217), *p*=0.019
capillary rarefaction (≤6/mm)	5.208 (1.062- 25.544), *p*=0.042	

pertension and less ANA and anti-centromere positivity. Risk for malnutrition was less frequent and scores of GI were lower in patients at early stage of disease. Severe skin involvement was shown to be related to very severe GI disease, capillary rarefaction was found to be an important determining factor for malnutrition and severe/very severe GI disease defined by using symptom based questionnaires.

The prevalence of malnutrition reported in different SSc cohorts was ranged from 15 to 55.6% according to different tools and definitions (13, 23-26). Lowest frequency was present according to low BMI (≤20 kg/m^2) or unvoluntary weight loss (24) and the highest one was according to one of the body composition derangements by using BIA (bioelectrical impedance analysis). Some of these studies demonstrated an association between malnutrition and disease activity (24, 26) or severity and mortality (26).

The MUST score, which is supposed to predict overall risk for malnutrition in chronic diseases, has been also studied in SSc. In a Canadian cohort including 586 SSc patients, 28.2% patients were at medium to high risk for malnutrition, MUST scores were shown to be related to shorter disease duration, diffuse cutaneous involvement and disease severity (13). Cereda *et al*. (27), demonstrated the highest prevelance of 54.4% at risk for malnutrition according MUST in 160 SSc patients and revealed an association between high nutritional risk and mortality. Two recent studies including 20.6% and 21% medium to high risk for malnutrition revealed an association between malnutrition and pulmonary involvement, the patients at high risk for malnutrition were found to have more frequently severe disease and lung involvement (14, 28). In our cohort, 15% of the patients were at medium to high risk for malnutrition, these patients were found to have less ANA and ACA, lower FVC and DLCO%, frequent lung involvement and pulmonary hypertension. Otherwise MUST score or BMI were not found to be related to cutaneous subset, usage of immunosuppressives, disease activity and severity.

The relationship between MUST scores and GI disease was evaluated in different studies; Baron *et al*. (13), found that MUST scores were associated with number of GI complaints namely poor appetite, early satiety, nausea, constipation and diarrhea. In the study of Caimmi *et al*. (28) including older patients with longer disease duration, MUST score was shown to be related to total UCLA GIT score. In our cohort, consisting of relatively younger patients with shorter disease duration; UCLA SCTC GIT 2.0 reflux scores were shown to be associated with weight loss score, however association was poor with overall risk for malnutrition. Nonetheless some studies did not show any relation between malnutrition and GI disease in SSc (24, 26, 29). So these two questionnaires should be used as complementary tools to define GI involvement and risk for malnutrition which might be related to different probable causes besides GI disease.

GI is frequently involved in SSc beginning after the early stages of disease and vasculopathy is thought to be one of the pathogenetic mechanism. The association between clinical vasculopathic manifestations and GI disease was investigated in different studies; DUs were found to be related to GI disease, predominantly lower oesophageal sphincter dysfunction, in 110 SSc patients who are at very early stage of disease (VEDOSS cohort) (30). Severe digital vasculopathy (digital ulcers, digital amputation) and cardiac involvements were shown to be frequent in patients who required parenteral nutrition due to severe GI disease in a different cohort (31). We evaluated the relationship between severity of GI disease, malnutrition and severe organ involvement. Severe skin involvement was found to be related to very severe GI disease which might be accused for malnutrition risk.

Severe capillaroscopic alterations were shown to be associated with severe disease, furthermore development of future severe organ involvement in two independent SSc cohorts (32, 33). We also evaluated the association between microvasculapathy and severity of GI disease and malnutrition; NVC late scleroderma pattern was frequnent in patients who are at medium to high risk for malnutrition, capillary raraefaction was found to be an important factor for malnutrition and severe/very severe GI disease. Microvasculopathy at digital circulation might be related to severity of GI disease and malnutrition in this SSc cohort independently of disease duration.

Our study has some limitations; it is a cross-sectional study and progression of GI and nutritional status by time was not traced. GI complaints were assessed by using a symptom based questionnaire and could not be supported by imaging methods. MUST might have some limitations in terms of reflecting the nutritional status in SSc patients, such as low prevalence of acute disease effect in SSc and not including some disease related factors which could influence the nutritional status (oral aperture, GI abnormalities, etc). The characteristics of this cohort, frequent

clinical vasculopathy (digital ulcers and PH) and severe NVC alterations, might facilitate to reveal an association between GI and malnutrition risk.

In conclusion; assessing GI complaints and nutritional status by using symptom based questionnaires plus BMI reflected the severity of GI disease and malnutrition in a SSc cohort along with including some limitations. Severe skin involvement and capillary rarefaction were the determining factors for malnutrion risk and severe GI disease independently of disease duration in this SSc cohort. Formal assessment and follow-up of GI severity and nutritional status should be included in standart of care for SSc patients which can be manupulated earlier by life style modification, nutritional intake, enteral and parenteral nutrition. Severity of organ involvement and NVC might be useful for clinicians to have an impression about SSc patients who are tended to have severe GI disease and malnutrition.

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