

Disease-related malnutrition in systemic sclerosis: evidences and implications

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ABSTRACT

The present review summarises evidences and provides recommendations for the screening and management of malnutrition in systemic sclerosis (SSc). This complication is frequently underestimated when assessing patients and this may lead to an impaired estimation of prognosis. The presence of malnutrition is indicated by anthropometric and biohumoral changes reflecting protein stores (low serum prealbumin) and influenced by organ involvement in SSc (skin and the gastrointestinal tract). Patients at high risk of malnutrition or with low prealbumin levels have shown increased mortality risk and, therefore, a nutritional assessment is mandatory in every SSc patient. This screening is especially important as malnutrition represents a potentially modifiable risk factor with nutritional interventions. The pillars of nutritional treatment are also discussed.

Introduction

Malnutrition is a frequent complication of many chronic diseases whose course and outcome is negatively affected by its presence (1). It is the result of the imbalance between protein-calorie requirements and nutrients intake to which three main factors can contribute at the same time: underfeeding, increased energy expenditure, and reduced nutrients availability/use (e.g. malabsorption). The inflammatory state that is often a pathophysiological component of acute and chronic disease is an important determinant of the imbalance in nutrients intake, as it is frequently responsible for both hyporexia/anorexia and increased energy requirements. Furthermore, diseases with a significant involvement of the gastrointestinal tract are more likely to result in nutritional status deterioration

(1-3). Systemic sclerosis is a chronic autoimmune disease with a complex pathogenesis (4). It affects skin and internal organs ultimately determining an excessive deposition of extracellular matrix resulting in organ damage. Autoimmunity and inflammation play a major role in fibroblast activation and endothelial dysfunction that are ideally possible in every tissue of the body (5). Most frequent organs involved include skin, lungs, the musculoskeletal system and finally, in up to 85% of patient cohorts, the gastrointestinal (GI) tract (6). Oesophageal dysfunction is present in about 85% of patients with SSc. Motility disturbances and lower oesophageal sphincter dysfunction are common features possibly resulting in gastro-oesophageal reflux, dysphagia, vomiting, regurgitation, oesophagitis or stricture (7, 8). In the small intestine, bacterial overgrowth due to luminal content stasis or decreased permeability secondary to intestinal fibrosis, may cause malabsorption. Functional derangements in SSc (e.g. oral aperture or disability) may also bring to a reduced food intake and overt malnutrition has been reported (9, 10). Until a few years ago, malnutrition was largely underestimated in SSc since it had been evaluated using heterogeneous criteria and studied in very small cohorts (11, 12). Evidence in this field has increased significantly and recent findings on its negative prognostic role suggest its systematic screening and identification in every setting of care (in- and outpatients) in order to prevent or correct it.

Prevalence of malnutrition in SSc and most relevant clinical associations

The first study to address a systematic approach to malnutrition in order to provide prevalence estimates was con-

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ducted by the Canadian Scleroderma Research Group (CSRG) (13). Using the “Malnutrition Universal Screening Tool” (MUST) for adults, validated by the British Association for Parenteral and Enteral Nutrition (BAPEN) (<http://www.bapen.org.uk/screening-for-malnutrition/must/introducing-must>), Baron *et al.* determined frequency and predictors of protein-energy malnutrition in a large cohort of Canadian SSc patients. MUST is based on three clinical parameters that have been associated with poor outcome: body mass index (BMI), unintentional weight loss (WL) in the previous 3–6 months and absent nutritional intake for more than 5 days. Each parameter is rated independently and the final total score (sum of the sub-scores from the three parameters) enables the evaluation of the overall risk of malnutrition as follows: 0 = low; 1 = medium; 2 = high (14). MUST is recommended by the European Society of Clinical Nutrition and Metabolism due to its high degree of reliability (low inter-observer variation) and association with outcome (14, 15). In this study 586 SSc patients were included, the vast majority of them being female (87%), with a mean age of 55 years and diffuse cutaneous involvement in 39%. The mean MUST score was 0.5 but when patients were categorised by its total score, 12.5% had a medium risk (MUST=1) and 17.4% of patients showed a high risk of malnutrition (MUST ≥2), a high figure in an understandably at risk population for malnutrition such as gastroenterology patients or hospitalised patients. Univariate logistic regression analysis in this cohort indicated that predictors of nutritional risk by MUST were: the number of GI symptoms, diffuse disease, shorter disease duration, disease severity (physician global assessment), oral aperture, haemoglobin, abdominal distension on examination, and the physician’s assessment of possible malabsorption. In multivariate analysis the number of GI complaints, disease duration and physician global assessment of disease severity independently predicted impaired nutrition status (13). Another method by which malnutrition has been investigated in SSc is bioelec-

trical impedance analysis (BIA) (16). BIA estimates the differing electrical conductivity of fat and lean tissue and measures the resistance and reactance, which allows calculating phase angle (PhA). PhA is a parameter describing the relationship between nutrition and hydration status and providing information on the health of soft tissues (higher values reflect higher cellularity, cell membrane integrity and better cell function), which has been associated with prognosis in different disease models (17). In a case-control study (124 SSc patients and 295 healthy matched volunteers), Krause *et al.* considered BMI calculation to rule out malnutrition and BIA to identify body composition derangements. According to BMI (<19 kg/m²), 13.7% of the SSc population were screened positive for malnutrition whereas PhA (<5°) revealed that 55.6% of patients had a pathologically impaired nutritional status. On a clinical level, PhA was only weakly inversely correlated with modified Rodnan skin scores and ESR. However, a positive relationship was found with Forced Vital Capacity % of predicted values. In this study antiPm/Scl antibodies and the diffuse cutaneous involvement were associated to low PhA as well as high Scleroderma Health Assessment Questionnaire (SHAQ) and NT-proBNP levels. As expected from this finding, patients with a reduced nutritional status more often presented cardiac involvement. This association has been confirmed in a recent Italian outpatient cohort (18) in which malnutrition, defined by a low BMI (<20 kg/m²) or unintentional weight loss (>5% in the last 3 months), was detected in 19% of the cohort and BMI values positively correlated with left ventricular mass (measured by echocardiography).

Our group also investigated the prevalence of malnutrition in 160 outpatients with SSc (19). We defined it as the presence of a BMI <20 kg/m² and/or a spontaneous weight loss ≥10% of body weight in the previous 6 months. Overall, 15% of patients were malnourished with both criteria being present in 17% of them. Single GI complaints were substantially unrelated to poor nutri-

tional status and only anorexia and early satiation appeared indicators of it. Among clinical parameters, only disease activity according to the criteria by Valentini *et al.* (20) was associated with malnutrition, while disease duration, GI involvement or cutaneous subset were not. This association was independent of other factors in multivariable analysis (1-point increase in score, odds ratio = 4.81 [95%CI, 2.45–9.44]). Besides, logistic regression showed a significant association with low serum prealbumin (<200 mg/L; odds ratio = 8.58 [95%CI, 2.27–32.34]). However, in the same cohort, when disease activity was taken into account along with anthropometric parameters in nutritional screening by MUST, we observed a consistent increase in nutritional risk (24.4% [95%CI, 17.4–31.3]) (21).

Finally, in another small North American investigation including 24 patients (22), the MUST but also the Subjective Global Assessment (SGA) – which is based on recent history of weight loss and changes in food intake, whether the patient feels malnourished and physical examination – were applied to determine the presence of malnutrition and its relationship to GI symptoms in SSc. In this study, health-related quality of life (HRQOL) and gastrointestinal tract severity were assessed using the University of California Los Angeles Scleroderma Clinical Trials Consortium Gastrointestinal Tract 2.0 (GIT 2.0)(23), a patient-reported tool investigating 7 domains (subscales: reflux, distention/bloating, diarrhoea, fecal soilage, constipation, emotional well-being, and social function) and which has been validated in different countries. The results of the study showed that moderate to severe malnutrition by the SGA (class B+C) and medium to high risk of malnutrition by MUST (≥1) were present in 50% and 37.5% of patients, respectively. There was a very small positive although not significant correlation between total GIT 2.0 scores and SGA while MUST levels of risk did not show any difference either in total or in subscale scores. Although, these data have been obtained from a very small number of patients with SSc with a wide spectrum of disease severi-

ty and duration, the study was powered enough to conclude that the assessment of the GI tract is not a reliable tool to predict malnutrition and validated GI clinimetry should be combined with at least one nutritional screening tool to comprehensively assess malnutrition in SSc patients. Furthermore, the study described laboratory data of haemoglobin levels, vitamin D, albumin or C-reactive protein levels across different categories of MUST or SGA but no significant association was found. The limited value of different biochemical parameters in nutritional assessment of SSc patients, has been also reported in the CSRG study cohort (24). Although, the MUST score was independently associated with lower albumin levels, this relationship accounted only for 7% of the variance of albumin in the model adjusted for disease severity. On the other hand, we have found that low serum prealbumin (<200 mg/L), despite being sensitive to different factors influencing its synthesis and degradation (*e.g.* adequacy of protein and energy intakes, inflammation, kidney function, etc.), was strongly associated with malnutrition independently of disease activity and food intake (19). It is reasonable that prealbumin could reflect the status of protein stores. These considerations support its potential usefulness as a early marker of malnutrition in SSc but further potential implication for patient management could be hypothesised, as in previous studies serum prealbumin was used to monitor the potential effectiveness of nutritional support (25).

Recommendations for malnutrition screening

All these evidences (summarised in Table I) point out that besides its clinical associations, malnutrition is a frequent complication of SSc that deserves its own assessment because it cannot be inferred solely by GIT involvement. Nowadays, in addition to guidelines for nutritional screening and management published by nutrition (national and international) societies a set of recommendations has been recently released by an expert panel from North America (12). Accordingly, the physician taking

Table I. Studies of the prevalence of malnutrition.

Author, year (reference)	Country	Patient population	Sample size	Criteria for malnutrition	Prevalence of malnutrition or high nutritional risk, % (95%CI)
Baron <i>et al.</i> , 2009 (13)	Canada	15-centre registry	586	MUST score ≥ 2	17.4% (14.4-20.7)
Krause <i>et al.</i> , 2010 (16)	Germany	Inpatients and outpatients	124	BMI <19 kg/m ² Phase angle <5°	13.7 % (8.2-21.0) 55.6% (46.5-64.6)
Caporali <i>et al.</i> , 2012 (19) & Cereda <i>et al.</i> , 2014 (21)	Italy	Outpatients	160	BMI <20 kg/m ² and/or 6-month WL $\geq 10\%$ MUST score ≥ 2	15.0 % (9.9-21.5) 24.4 % (17.4-31.3)
Murtaugh <i>et al.</i> , 2013 (22)	USA		24	MUST score ≥ 2 SGA class = C	29.2 % (12.6-51.1) 50.0 % (29.1-70.9)
Rosato <i>et al.</i> , 2014 (18)	Italy	Outpatients	94	BMI <20 kg/m ² 3-month WL >5%	19.2 % (11.8-28.6) 5.3 % (1.8-12.0)

BMI: body mass index; MUST: Malnutrition Universal Screening Tool; SGA: Subjective Global Assessment; WL: weight loss.

Table II. The “Malnutrition Universal Screening Tool” (MUST).

Question	Score
Body mass index (BMI):	
>20 kg/m ²	= 0
18.5–20.0 kg/m ²	= 1
<18.5 kg/m ²	= 2
Weight loss during the previous 3-6 months:	
<5%	= 0
5–10%	= 1
>10%	= 2
Acute disease ^a or absent nutritional intake ≥ 5 days:	
Absent	= 0
Present	= 2
Total score:

^aIt should be marked as present when disease activity according to the criteria by Valentini *et al.* (20) is scored ≥ 3 (20).

care of the SSc patient should screen for the presence of GI involvement and malnutrition. In respect to nutritional derangements, the use of multi-dimensional screening tools should be considered and preferred. Although the MUST is one of the many other screening tools available and it was not specifically validated for SSc patients it is the only one to have been extensively studied in SSc. Nonetheless, besides relying primarily on anthropometric measurements, such as BMI and WL, we recently performed a validation study (21) with MUST incorporating data of SSc-specific disease activity according to the Valentini's scoring system, a multi-domain questionnaire which includes data from the skin, cardiovascular, gastrointestinal involvement and labora-

tory parameters of inflammation (ESR) and complement (20). Acute disease in our study was considered using a validated score in SSc (Valentini's disease activity score ≥ 3) and this complemented the evaluation of nutritional intake. This adjustment led us to improve our detection of high-risk patients (score ≥ 2) (from 9.4% with the simple MUST to 24.4%). High nutritional risk by MUST (≥ 2) is an indication to nutritional intervention. Nevertheless, active monitoring is strongly recommended in presence of moderate risk (MUST = 1) in order to prevent nutritional deterioration (see Table II). Overall prevalence of high nutritional risk in SSc in current literature is estimated being around 20% (Fig. 1).

Finally, expert recommendations in-

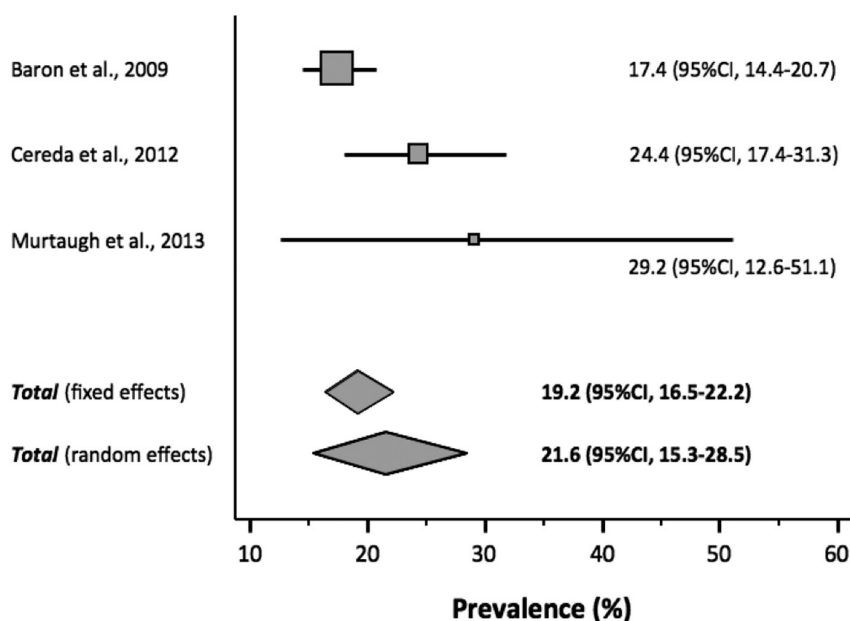


Fig. 1. Meta-analysis of estimates of high nutritional risk by MUST in SSc.

clude a set of laboratory parameters to comprehensively evaluate nutrition status: hemoglobin levels, serum carotene, serum folate, serum albumin, which we feel should be integrated by prealbumin. Other tests such as serum methylmalonic acid, zinc, 25-OH vitamin D levels, vitamin K level or prothrombin time (PT), C14 xylose breath test or a hydrogen breath test should be ran when malabsorption is suspected and this is a relatively frequent condition in SSc where a high proportion of patients suffer from severe bacterial overgrowth (12, 26).

Prognostic value of malnutrition

Regardless of the definition of malnutrition in different surveys of SSc patients and which screening tool is selected to monitor cohorts, recent observations from prospective studies point out that the identification of an impaired nutritional status is a relevant factor in SSc prognostic stratification. Krause *et al.* (14) have performed a longitudinal analysis on 111 SSc patients followed up for a mean time of 35.2 months (SD 7.3). Eleven of these patients (10%) died of SS-related causes and the proportion of those in the group presenting impaired body composition (with low PhA) was significantly higher than those with a preserved nutritional status. Of note, BMI values did not show

any association with survival in this study.

A longitudinal investigation of a cohort of SSc outpatients was also performed by our study group (in press). We found mortality was associated to high nutritional risk by MUST. In our cohort, similarly to what described by Krause *et al.* (14), BMI and recent weight loss were not associated with mortality (HR=2.8 [95%CI, 0.6–13.2]). However, disease activity was a significant predictor of survival (HR=6.3 [95% CI, 1.8–21.7]) and when incorporated into MUST the association between mortality and high nutritional risk (HR=8.3 [95% CI, 2.1–32.1]) was improved. Furthermore, we have recently performed a longitudinal multicentre study on 299 SSc outpatients to evaluate the value of prealbumin and nutritional derangements in predicting mortality (in press). After a median follow-up of 48 (25–58) months, 11% of patients had died. Again, poor nutritional status defined by BMI and weight loss was only marginally associated with reduced survival (HR=2.52 [0.65–9.75]). However, low serum prealbumin (<200 mg/L) significantly predicted mortality. Interestingly, prealbumin retained its prognostic role even after adjusting for other significant disease-related predictors. In particular, we reported a striking difference (more than 3-fold in both cases)

among incident rates of mortality in those without significant organ involvement or with no or just one comorbidity but with different prealbumin concentrations arguing in favor of the added value of prealbumin in these cases and their prognostic stratification.

Altogether these results point out the relevance of detecting nutritional derangements in the routine assessment of SSc patients.

Nutritional interventions in SSc

Impaired nutritional status not only is a predictor of worse outcome but also a potentially modifiable factor. Based on the outcome of nutritional screening procedures, all patients screened positive for either moderate or high nutritional risk (MUST ≥ 1) should be referred to a clinical nutrition specialist (dietician and clinical nutritionist) for, deeper evaluation, nutritional intervention and monitoring. Nowadays, in agreement with national and international guidelines (25–27), nutritional counseling has to be considered as the first-line strategy. Counselling is currently defined “as use of an interactive helping process focusing on the needs, problems, or feelings of the patient and significant others to enhance or support coping, problem solving, and interpersonal relationships” and nutritional counselling focuses on the need for diet modification, consistently with individual preferences, ethnicity and culture. Focusing on practical advices on how to manage meals (volume, frequency, quality and texture), it would allow improving food intake by coping in several cases with most GI complaints or complications such as xerostomia, oropharyngeal and oesophageal dysphagia, gastroesophageal reflux, oesophageal stricture, small bowel distention and bloating, constipation and diarrhoea. Unfortunately, no specific diet for SSc patients has been investigated and could be recommended and suggestions rest on limited evidence mostly collected in other populations of patients. In case of unsatisfactory protein-calorie intake the use of energy-dense oral nutritional supplements should be considered. However, in some cases dietary modifications are not effective

or are not likely to allow the covering of estimated requirements, and artificial nutritional support becomes necessary. This approach definitely depends on patient's willingness, potential risk and expected benefits. Indeed, enteral nutrition (total or integrative enteral tube feeding) is the first choice as continuing use of the small intestine allows metabolising nutrients more efficiently by the body, maintaining immune-competence and preventing infectious complications and organ malfunction. If enteral nutritional support is not feasible due to gut dysfunction (malabsorption) parenteral nutrition is an effective intervention for delivering nutritional support.

Conclusions

SSc is a complex and heterogenous connective tissue disease requiring delicate management of its numerous complications. Malnutrition is one of them and given its prognostic negative implications it should be included in the routine assessment of every SSc patient. Anthropometric (BMI, weight) and serum biomarkers (prealbumin) are key elements in both baseline assessment and follow-up evaluations. In SSc gastrointestinal involvement is a contributing factor to nutritional derangements but it also challenges therapeutic interventions. Specific trials evaluating the best approach to overcome these difficulties are lacking in SSc and should be performed to better inform the clinician in the routine approach to this comorbidity.

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