Nutritional Decline in Scleroderma Patients
Data from a single Romanian center

ALEXANDRA BURLUI[1,2]*, MARIANA GRAUR[1,3], DANIELA CONSTANTINESCU[1], ANCA CARDONEANU[1,2], LUANA ANDREEA MACOVEI[1,2], ELENA REZUS[1,2]

[1]Grigore T. Popa University of Medicine and Pharmacy, Faculty of Medicine, 16 Universitatii Str., 700115, Iasi, Romania
[2]Clinical Rehabilitation Hospital, 1st Rheumatology Clinic, 14 Pantelimon Halipa Str., 700661, Iasi, Romania
[3] Sf. Spiridon Clinical County Emergency Hospital, Diabetes, Nutrition and Metabolic Diseases Clinic, 1 Independenței Blvd., 700111, Iasi, Romania

Malnutrition has been known to provide poor survival outcomes in systemic sclerosis (SSc). We recruited a series of 40 consecutive SSc patients, 22 (55%) with limited cutaneous involvement and 18 (45%) with the diffuse form of disease. The study group was evaluated using the modified Rodnan skin score (mRSS), anthropometric measurements, the EPIC-Norfolk Food Frequency Questionnaire, the Malnutrition Universal Screening Tool (MUST) as well as circulating albumin and vitamin D. MUST scores were correlated with mRSS and serum albumin (R=0.40, p=0.010, and R=-0.46, p=0.003, respectively). Serum vitamin D values were inversely related to mRSS (R=-0.35, p=0.026). We recorded a greater number of daily gastrointestinal symptoms associated with diets rich in sodium, fat, sugars and snacks, carotene, and á-tocopherol equivalents (vitamin E) in our study population. Scleroderma patients might benefit from nutritional counseling in order to follow a diet tailored to their specific needs.

Keywords: systemic sclerosis, malnutrition, diet, vitamin D.

Systemic sclerosis (SSc) is a rare connective tissue disease accompanied by multi-system involvement and considerable morbidity and mortality. Disease pathogenic mechanisms involve immune, vascular and neural changes as well as a widespread fibrosis of the skin and visceral organs [1-3]. Food-related behavior (including the ability to procure and process food) is challenged by the severe hand disability resulting from extended skin fibrosis and joint contractures in scleroderma [4].

The progressive deposition of extracellular matrix proteins causes a substantial loss of function affecting organs such as the skin, lungs, and kidneys. Disease-related changes involve the gastrointestinal (GI) tract in its entirety in up to 90% of cases [4,5]. SSc patients develop microstomia, xerostomia, edentation, dysphagia, and acid reflux, as well as gastroparesis and consecutive early satiety [6-8].

Intestinal dysmotility and dysbiosis are also potential risk factors for body composition hindrance in scleroderma patients. Moreover, exocrine pancreatic insufficiency together with bacterial overgrowth may lead to malabsorption, subsequent fat-soluble vitamin deficiencies and weight loss [1,9,10].

Vitamin D is fat-soluble and was found low in patients with SSc regardless of seasonal sun exposure or cholecalciferol supplement intake [11,12]. Decreased serum 25-hydroxyvitamin D (25(OH)D) is thought to associate with immune disturbance as well as organ involvement, bone density and microvascular changes in patients with systemic sclerosis [11-16].

Prealbumin is independently correlated with disease activity and malnutrition in scleroderma [17,18]. Research addressing malnutrition also used serum albumin for the assessment of nutritional status with various, discrepant results [19,20].

As yet, studies used scoring systems such as the Malnutrition Universal Screening Tool (MUST), Mini Nutritional Assessment (MNA), University of California Los Angeles Scleroderma Clinical Trials Consortium Gastrointestinal Tract Questionnaire (GIT 2.0), and Subjective Global Assessment (SGA) in order to estimate gastrointestinal involvement and risk of malnutrition in patients with scleroderma [4,21-23].

Commonly, dietary analysis implies the use of food diaries, 24h dietary recall and food frequency questionnaires [10,17]. A validated and adapted Romanian version of the food frequency questionnaire used by the European Prospective Investigation into Cancer and Nutrition Norfolk (EPIC-Norfolk) is currently available [24].

Experimental part

Material and method

Our study aimed to investigate the relationship between the extent of skin involvement, nutritional status, the risk of malnutrition, and two serum markers (circulating albumin and vitamin D) in patients with systemic sclerosis. Secondary objectives included a detailed analysis of scleroderma patients' diet and food-related behavior.

We conducted a cross-sectional study in which we recruited 40 adult patients with systemic sclerosis over a period of three months. All participants fulfilled the European League Against Rheumatism (EULAR) 2013 diagnosis criteria for systemic sclerosis and were classified as diffuse cutaneous (dcSSc) or limited cutaneous SSc (lcSSc) according to LeRoy. None of the patients in our study population were under parenteral support. We recorded anthropometric data such as body mass index (BMI), waist circumference and waist/hip ratio as well as the number of daily gastrointestinal (GI) symptoms and unintended weight loss within 6 months prior to the study. We evaluated Malnutrition Universal Screening Tool (MUST) and food-related behavior in all patients.

We applied the validated and adapted Romanian version of the EPIC-Norfolk Food Frequency Questionnaire to achieve a detailed evaluation of patients' diet. We entered

* email: alexandra.burlui@yahoo.com; Phone: +40722313189

the data regarding average food consumption during the previous year in the FETA dietary assessment software (version 2.53).

Biological samples (venous blood) were collected in order to investigate circulating vitamin D levels and albumin. We assessed vitamin D values using a solid phase Enzyme Linked Immunosorbent Assay performed on microtiterplates (25OH Vitamin D Total ELISA 90', DIAsource ®). The first step consisted of incubation at room temperature for 60 minutes. During this time, vitamin D present in calibrators (D2 and D3) was separated from binding proteins in order to attach to binding sites of specific monoclonal antibodies. The first washing step was followed by a competition reaction involving a fixed amount of vitamin D (labeled with biotin in the presence of horseradish protein) which competes with unlabelled vitamin D (D2 and D3) fixed on the monoclonal antibody binding sites. The samples were incubated for 15 minutes, at room temperature. The competition reaction was then stopped through the washing of the microtiterplates and the addition of Stop Solution. Consequently, the microtiterplates were read at a suitable wavelength. The measurement of absorbance through the colorimetric method was able to identify the quantity of substrate turnover, knowing that absorbance is inversely proportional to vitamin D concentration. Total vitamin D values present in the samples was determined by dose interpolation from the calibration curve.

We measured serum albumin levels through spectrophotometry (bromocresol green reaction in acid environment, BioSystems®).

The statistical analysis of the data was performed using Microsoft Office Excel and IBM SPSS Statistics v20 for Windows. The differences between patient subgroups were assessed through *student t-test* or *ANOVA*. We established relationships between variables using *Pearson R* and *Spearman's* correlation coefficients. Statistical significance was set at $p<0.05$.

The local Ethics Committee granted its approval for the current study. All subjects signed an informed consent beforehand.

Results and discussions

We included 40 patients, of which 34 women and 6 men (F:M=5.6:1) aged between 25 and 83 years (54±29 years). Our study population was composed of 22 patients with lcSSc (55%) and 18 patients with dcSSc (45%). The clinical and biochemical characteristics of the study group are shown in table 1. Serum vitamin D was deficient (<20ng/mL) in 38 patients (95%). Albumin levels were below normal in 4 patients (10%) and low-normal in 9 study participants (22.5%).

We identified mRSS score values ≥20 in 9 patients (22.5%). The degree of skin involvement was strongly associated with the diffuse cutaneous form of disease (R=0.66, p<0.001), with a statistically significant difference between lcSSc and dcSSc (p=0.043). The discrepancies in terms of unplanned weight loss recorded during the 6 months prior to the study were not statistically significant according to disease phenotype. Other parameters such as BMI, waist circumference, waist/hip ratio and serum biomarkers were also similar across the two groups.

In our study population, 29 patients were eutrophic (72.5%), 4 (10%) were underweight, 2 (5%) overweight and 5 (12.5%) obese.

MUST values identified 6 participants at high risk (15%) and 4 patients at medium risk for poor nutrition (10%). Scores were significantly higher in dcSSc patients (p=0.033).

The majority of patients (33, 82.5%) reported the occurrence of daily GI symptoms. The extent of skin involvement was strongly correlated with digestive symptoms regardless of disease phenotype (R=0.534, p<0.001). We detected a negative correlation between serum vitamin D and mRSS (R=-0.35, p=0.026) (fig. 1). Statistical analysis showed no relevant relationships between circulating 25(OH)D levels and other parameters.

Biochemical assessment revealed associations between serum albumin and weight (R=0.49, p=0.001), BMI (R=0.53, p<0.001) as well as waist/hip ratio (R=0.37, p=0.019) (fig. 2). Albumin and BMI were inversely correlated with MUST scores (R=-0.46, p=0.003, and

	Mean	Minimum	Maximum	Std. Deviation
Age (years)	52.17	25	83	14.27
mRSS	12.90	2	41	9.25
BMI (kg/m2)	23.70	16.14	33.40	4.23
Waist circumference (cm)	82.85	64	121.00	13.27
Waist/hip ratio	0.81	0.66	1.11	0.08
Weight loss (kg)	2.90	0.00	24.00	5.29
Serum vitamin D (ng/ml)	10.51	2.52	33.89	6.56
Serum albumin (mg/l)	39.38	32.30	54.70	4.20

Table 1
CLINICAL AND BIOCHEMICAL CHARACTERISTICS OF THE STUDY GROUP

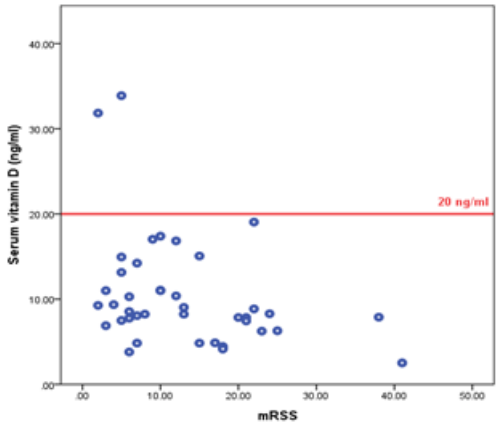

Fig. 1. Correlation between serum vitamin D levels and mRSS

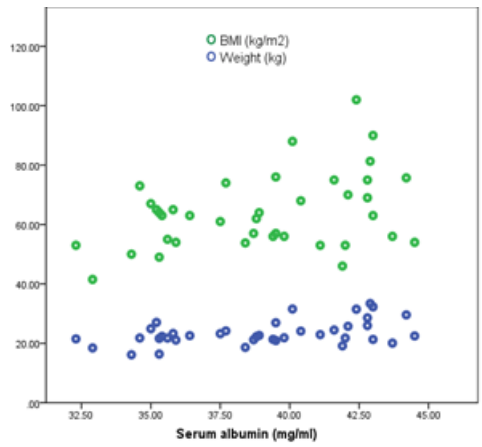

Fig. 2. Correlation between serum albumin levels, BMI, and weight

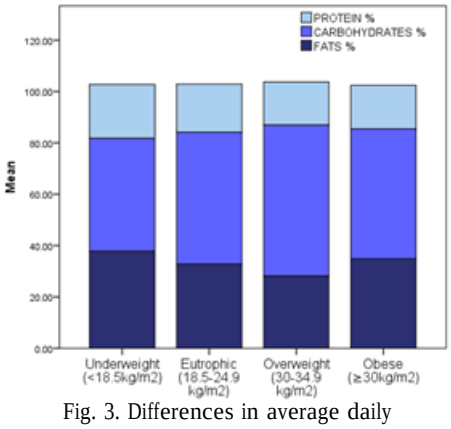

Fig. 3. Differences in average daily macronutrient intake according to BMI

Table 2

SIGNIFICANT CORRELATIONS FOR DAILY DIGESTIVE SYMPTOMS

	R	p
mRSS	0.53	<0.001
Fat (g)	0.43	0.006
Protein (%)	-0.33	0.039
Cholesterol (g/day)	0.33	0.037
Alpha tocopherol equivalents (mg/day)	0.48	0.002
Alcohol (g/day)	-0.35	0.028
Sugars, preserves and snacks (g/day)	0.37	0.033
Carotene equivalents (mcg/day)	0.31	0.049
Iodine (mcg/day)	0.34	0.030
Manganese (mg/day)	0.36	0.024
Sodium (mg/day)	0.35	0.029

R=-0.45, p=0.004, respectively). MUST values were also linked to the extent of skin fibrosis (R=0.40, p=0.010).

Data provided by the EPIC-Norfolk Food Frequency Questionnaire showed insufficient energy uptake according to age and gender in 24 patients (60%). When classified according to BMI, patients displayed relevant differences in mRSS values (p=0.030), serum albumin (p=0.004) and MUST scores (p<0.001).

The ANOVA testing failed to reveal significant discrepancies in terms of daily caloric intake (p=0.286) or dietary protein (p=0.332), carbohydrates (p=0.172), and fat (p=0.267) in relation with BMI (fig. 3). The same was found for circulating vitamin D (p=0.825), reported weight loss (p=0.568), and GI symptoms (p=0.211). There were no significant differences with respect to energy or macronutrient uptake between patients who were symptomatic for GI involvement and asymptomatic individuals.

Although normal in the majority of patients, serum albumin levels were lower in the underweight group (p=0.035).

Additionally, we uncovered a greater number of daily gastrointestinal symptoms associated with diets rich in sodium, fat, sugars and snacks, carotene and α-tocopherol equivalents (vitamin E) (table 2). Fiber and carotene consumption correlated with unplanned weight loss (p=0.001, and p=0.002, respectively). A higher percentage of dietary protein was linked to fewer GI symptoms.

Malnutrition risk did not correlate with age, macronutrient intake or reported GI involvement. Patients with MUST scores ≥ 2 exhibited more severe weight loss (p<0.001), lower BMI and waist circumference (p=0.006 and p=0.021, respectively), decreased total energy intake (p=0.006), lower serum albumin (p=0.003), and higher dietary fiber consumption (p=0.014) compared to the rest of the group.

We found no association between gastrointestinal symptoms in our study population and night eating, the number of meals consumed daily, binge-eating, late suppers or TV viewing during meals. However, sleep deprivation was significantly correlated with higher caloric uptake (R=0.33, p=0.036).

Scleroderma-related impairment of the GI tract is known to contribute substantially to body composition derangements. Considering the mortality risk associated with malnutrition in systemic sclerosis, nutritional decline in these patients is beginning to attract interest from researchers [1-3,21].

It has been shown that a BMI lower than 18.5kg/m^2 indicates protein-energy malnutrition as well as poor survival outcome in scleroderma [1,3,22]. Obesity is known to associate with a higher risk for cardiovascular disease [25]. However, obesity was infrequent in our study population.

Statistical analysis did not identify a significant relationship between vitamin D intake (diet or supplements) and circulating 25(OH)D, similar to previously published results [12]. Contrary to conclusions drawn in other similar studies, serum vitamin D levels were correlated with mRSS, but not patients' age in our study group [12,26].

MUST was developed by the British Association for Parenteral and Enteral Nutrition (BAPEN) in order to evaluate the risk of malnutrition in adult populations. The Canadian Scleroderma Research Group (CSRG) used MUST scores in a cohort of 586 patients and found significant associations with oral aperture size and early satiety [21]. MUST values did not correlate with the number of daily GI symptoms reported in our study population but were significantly associated with the diffuse form of disease. As opposed to other findings, serum albumin was linked to MUST in our patients [1,19,21]. Nonetheless, malnutrition evaluated by this tool may be underestimated in systemic sclerosis [1,22].

We found no relevant differences in terms of energy or macronutrient uptake between symptomatic and asymptomatic patients with respect to digestive symptoms. Although the assessment was done through a 3-day food record questionnaire, results were similar in a previously published study [9]. Interestingly, daily caloric intake, as well as the percentage of dietary protein, carbohydrates, and fat did not differ across BMI classes. A similar energy and protein uptake in well-nourished and malnourished patients was also reported by *Caporali et al.* [18].

Gastrointestinal symptoms were frequent in our study population (82.5%) irrespective of disease phenotype and comparable to other studies [4,27]. Certain foods might either perpetuate or facilitate the appearance of disease-related digestive manifestations in systemic sclerosis [9]. Oxidative stress is believed to boost the activation of scleroderma patients' fibroblastic cells as well as differentiation to myofibroblasts. Carotene and α-tocopherol are known to be potent intracellular antioxidants [28]. Our study found that carotene and α-tocopherol equivalents were associated with GI symptoms regardless of disease form or the extent of cutaneous involvement. The same was true for diets rich in sugars and snacks, fat, and sodium. Contrarily, a higher percentage of dietary protein was correlated with a decreased number of daily GI symptoms.

Despite its known gastric irritant properties, alcohol was inversely associated with GI manifestations possibly due to decreased consumption in symptomatic patients.

It has been shown that systemic sclerosis patients may present with fructose malabsorption [10]. We identified no significant association between scleroderma-related GI manifestations and dietary fructose, glucose, lactose, maltose or galactose. Nevertheless, a diet low in Fermentable Oligosaccharides, Disaccharides, Monosaccharides and Polyols (low-FODMAP) could be beneficial in reducing scleroderma-related GI symptoms [10].

Conclusions

The present research found several risk factors for nutritional decline in patients with scleroderma. Together with an unbalanced diet, disease phenotype and activity, the severity of gastrointestinal involvement may influence systemic sclerosis patients' nutritional status with possible consequences on quality of life and prognosis.

To our knowledge, this is the first study to use the EPIC-Norfolk Food Frequency Questionnaire in scleroderma. More than half of our study population exhibited subnormal daily caloric uptake. In addition, we found an alarming 10% underweight patients. The risk of malnutrition estimated by the MUST score was associated with lower BMI and total energy intake. While the most part of our patients were eutrophic, a number of risk factors for body composition abnormalities were found in all participants. However, dietary assessment in the present research implied a comparison with normal values recommended for healthy individuals of the same age and gender.

We obtained a strong correlation between mRSS values and gastrointestinal symptoms in our study group. Moreover, a relationship between circulating 25(OH)D and the degree of skin involvement was detected in both lcSSc and dcSSc. Vitamin D values were low in 95% of our study population regardless of dietary and supplement intake.

Serum albumin levels were found to be normal in the majority of patients, but lower in the underweight group. Additionally, they correlated with MUST scores, contrary to results obtained by other research teams.

Scleroderma patients might benefit greatly from nutritional counseling in order to follow a diet tailored to their specific needs. Bearing in mind the potentially severe disease-related gastrointestinal involvement and subsequent high risk for malnutrition, the need for defining the characteristics of a balanced diet in systemic sclerosis, the implementation of dietary interventions as well as routine screening for malabsorption are of major importance.

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