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Adherence to the Mediterranean Diet in Italian Patients With Systemic Sclerosis: An Epidemiologic Survey

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Objective. Systemic sclerosis (SSc) is an orphan disease that can lead to severe involvement of the gastrointestinal tract with a significant impact on patients' quality of life (QoL). The Mediterranean diet (MD) was consistently demonstrated to have beneficial effects on chronic diseases based on biological bases. We aimed to evaluate the adherence to the MD of Italian patients with SSc to preliminarily assess its association with gastrointestinal symptoms and other disease features, mood, and QoL.

Methods. In this cross-sectional study, adherence to the MD was measured in 387 patients from four SSc Italian referral centers through the 14-item Mediterranean Diet Adherence Screener (14-MEDAS) questionnaire. We also registered patients' reported outcomes related to the QoL and mood.

Results. Overall, an optimal adherence to MD was observed in 14.7% of patients with SSc, a moderate adherence in 71.3%, and a low adherence in 14.0%. In univariate analysis, poor adherence to the MD was associated with a more prominent depressive mood, time missed at work, and perception of more severe Raynaud's phenomenon and digital ulcers, whereas the 14-MEDAS score inversely correlated with depression score and reflux.

Conclusion. In our cohort of patients with SSc, overall adherence to MD was moderate. Patients with lower adherence to MD also reported worse outcomes related to QoL and mood. Administration of the 14-MEDAS could be a reasonable choice to assess adherence to the MD in patients with SSc. Future initiatives to study the role of MD in the management of patients with SSc are warranted.

INTRODUCTION

Systemic sclerosis (SSc) is an autoimmune disease characterized by small vessel vasculopathy, autoantibody production, and fibrosis of the skin and internal organs. It is an uncommon and clinical heterogeneous illness, designated as an orphan disease, because of the multiple unmet clinical needs and lack of effective therapies.¹ Typical clinical features include Raynaud's phenomenon and skin fibrosis. Digital ulcers and progressive

involvement of internal organs occur frequently and account for the high burden in terms of morbidity and mortality.²

The gastrointestinal (GI) system involvement is frequent in SSc and significantly impacts patients' quality of life (QoL) and clinical status.³ Regrettably, diagnostic tools to precisely assess SSc-related GI involvement are lacking, and current therapeutic strategies are still limited as no immunosuppressive or antifibrotic therapy is effective in treating this disease domain. Reducing symptoms, preventing local complications, and maintaining

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adequate nutrition are the supportive standard measures for GI disease.⁴

It has been suggested that controlled dietary intervention and nutritional support may positively impact symptoms and QoL and prevent progressive debilitation in patients with SSc.⁵ Nevertheless, the evidence regarding feeding habits and the role of specific dietary patterns in SSc is currently limited.

For instance, a study on a small Swedish cohort of patients with SSc observed that although patients with SSc had a similar intake of macronutrients and energy compared with healthy controls, they had a significantly lower intake of dietary fibers and suggested that GI and extra-GI SSc features are likely to influence the patients' feeding and dietary habits.⁶ Another report on 42 patients with SSc living in a non-Mediterranean area who underwent a dietary and nutritional assessment through a food frequency questionnaire (FFQ) and the Malnutrition Universal Screening Tool showed a high sodium intake and frequent sub-optimal energy consumption in the study group.⁷

Because SSc implies a subversion of the intestinal barrier and the gut-microbiota balance, it could be speculated that dietary intake influences the degree of GI involvement and its phenotypic expression. Indeed, intestinal dysbiosis has been broadly reported in SSc and linked to disease characteristics and nutritional status.^{8,9} Preliminary evidence has shown improvements in patient-reported GI symptoms after intervention with probiotic therapy and a low fermentable oligosaccharides, disaccharides, monosaccharides, and polyol diet, but not following tailored dietary and nutritional counseling.¹⁰ However, a low fermentable oligosaccharides, disaccharides, monosaccharides, and polyol diet did not appear to be associated with specific microbiota characteristics or reduced GI symptoms in a recent cross-sectional study on 66 patients with SSc.¹¹

The Mediterranean diet (MD) is considered by the United Nations Educational, Scientific, and Cultural Organization as an "intangible cultural heritage of humanity," encompassing a set of knowledge, skills, and traditions related to food production and consumption typical of the Mediterranean populations.¹² In its most plain sense, it refers to a dietary pattern typical of the lands surrounding the Mediterranean basin, founded on a significant intake of olive oil, cereals, legumes, fruits, and vegetables, moderate consumption of dairy products and wine, and preferential use of fish over others meat products.¹³ From a clinical point of view, the evidence accumulated so far has demonstrated a beneficial effect of adherence to MD concerning cardiovascular disease. A broader positive role has been suggested in preventing metabolic syndrome and various types of cancer.^{14,15}

Postulated biologic mechanisms to explain the beneficial impact of this food habit included protection against inflammation, oxidative stress, platelet aggregation, and microbiome-mediated production of mediators influencing metabolic status.¹⁶ In rheumatoid arthritis, the MD seems to play a role in reducing pain and increasing physical function with a high intake of

monounsaturated fatty acids, a component of the MD score, being indicated as the primary determinant of inflammation suppression.^{17,18}

The present study aimed to evaluate adherence to the MD in an Italian multicenter cohort of patients with SSc. Moreover, we preliminarily assessed the association between MD adherence and GI symptoms and other disease features, mood, and QoL and the feasibility of measuring MD adherence in such patients.

METHODS

Participants. Consecutive adult patients who fulfilled the 2013 American College of Rheumatology/EULAR classification criteria for SSc¹⁹ were enrolled between April 2019 and May 2021 during their programmed follow-up visits in four scleroderma referral centers covering the three geographical macro-areas in Italy, namely Northern (NI), Centre (CI), and Southern Italy (SI). The patients enrolled in the survey did not specifically undergo dietary counseling within their follow-up program for SSc.

Ethics approval. The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committees of the coordinating center (ie, IRCCS Ospedale San Raffaele [protocol code IMMUNORADAR DSAN 1178/9, March 8, 2018]), and of all collaborating centers (Humanitas Research Hospital of Rozzano, Fondazione Policlinico Universitario A. Gemelli IRCCS of Rome, and Ospedale San Carlo of Potenza). Written informed consent was obtained from all subjects involved in the study.

Clinical evaluation and questionnaires. In this cross-sectional study, a total of 387 unselected patients from four SSc Italian tertiary care centers were involved. The explanation of the study and the enrollment of the patients, as well as the administration of the survey, took place during the same scheduled outpatient follow-up visit.

At enrollment, the medical history was reviewed for each patient, including comorbidities and therapy. Disease duration was defined as years from the first disease manifestation other than Raynaud phenomenon. The severity of cutaneous involvement was assessed with the modified Rodnan Skin Score. Patients were classified into limited and diffuse cutaneous subsets according to Leroy's definition,²⁰ taking into account their disease history. The presence of SSc-related interstitial lung disease and pulmonary arterial hypertension was determined based on historical instrumental findings on chest computed tomography and right heart catheterization, respectively. For all patients, the last routine instrumental determinations for forced vital capacity, carbon monoxide diffusing capacity, and pulmonary artery systolic pressure were noted. The median time from the last pulmonary function test and echocardiography was 7.0 (3.4–8.0)

and 9.1 (4.4–10.4) months, respectively. Historical determination for the presence of antinuclear antibodies and autoantibodies against extractable nuclear antigens specific for SSc were registered. To assess the study's primary objective, we administered to all participants the 14-item Mediterranean Diet Adherence Screener (14-MEDAS).²¹ The questionnaire consists of 14 items related to Mediterranean dietary patterns (12 questions on food consumption frequency and 2 questions on food intake habits). Each question of the MEDAS questionnaire is scored 0 or 1, producing a derived score ranging from 0 to 14. In a previous study from the questionnaire authors, it has been suggested that a score of less than or equal to 5 points indicates low adherence, 6 to 9 indicates moderate adherence, and greater than or equal to 10 points indicates a high level of adherence to the principles of the MD.²² Recently, MEDAS has been validated in an adult population from Italy in a cross-national study.²³ The 14 questions of the tool, as well as the criterion and logic for scoring, are openly accessible in the manuscripts from the questionnaire's original authors.^{21,22}

The following validated instruments were administered to all patients to assess the prevalence and the severity of GI symptoms, the risk for depression and anxiety disorder, and the impact of the disease on the quality of life and work: (1) the University of California at Los Angeles (UCLA) Scleroderma Clinical Trial Consortium (SCTC) GI Tract (GIT) 2.0 questionnaire,²⁴ (2) the Reflux Disease Questionnaire,²⁵ (3) the Hospital Anxiety and Depression Scale (HADS),²⁶ (4) the Scleroderma Health Assessment Questionnaire, (SHAQ)²⁷ and (5) the Work Productivity and Activity Impairment questionnaire.²⁸ Weight and height were measured to calculate the body mass index.

Statistical analysis. Data were analyzed using SPSS Statistics version 26.0 for Windows (IBM). The normality in the data distribution was verified by combining the evaluation of the Q-Q diagram and the Shapiro-Wilk test. The categorical variables were described as numbers and percentages, whereas the continuous quantities as mean \pm SD or median and interquartile range (25%–75%) were based on the data distribution. Chi-square, Mann-Whitney, or Kruskal-Wallis tests were used according to data type and distribution. Correlations between continuous variables were studied by Spearman's rank. The strength of the correlation was expressed through the r coefficient. P values were adjusted according to the Benjamini-Hochberg method to control for type I errors. The significance level (α) was set at 0.05.

RESULTS

Adherence to the MD. Demographic and clinical characteristics of patients with SSc are reported in Table 1. According to 14-MEDAS, 54 patients (14.0 %) had low adherence, 276 (71.3 %) had moderate adherence, and 57 (14.7 %) had high adherence to the MD. The mean score for the entire cohort was

Table 1. Demographic and clinical characteristics of patients*

	Patients with SSc (n = 387)
Geographical area	
Northern Italy, n (%)	157 (40.6)
Central Italy, n (%)	94 (24.3)
Southern Italy, n (%)	136 (35.1)
Age, mean \pm SD, years	55.6 \pm 13.9
Disease duration, mean \pm SD, years ^a	9.4 \pm 7.2
Female, n (%)	366 (94.6)
Body mass index, mean \pm SD	23.7 \pm 4.4
Body mass index	
<18.5, n (%)	19 (4.9)
\geq 18.5 and <25, n (%)	234 (60.5)
\geq 25 and <30, n (%)	90 (23.3)
\geq 30, n (%)	44 (11.3)
Overlap with others CTDs, n (%)	23 (5.9)
ACA/ATA, n (%)	138 (35.6) / 137 (35.4)
Diffuse cutaneous SSc, n (%)	123 (31.7)
Modified Rodnan skin score, median (IQR)	3.0 (2.0 – 7.0)
Digital ulcers (ever), n (%)	88 (22.7)
Interstitial lung disease (HRCT), n (%)	116 (30.0)
FVC, %, mean \pm SD	101.9 \pm 19.8
DL _{CO} , %, mean \pm SD	72.3 \pm 19.5
Pulmonary arterial hypertension (RHC), n (%)	2 (0.5)
PASP, mm Hg, median (IQR)	28.5 (25.0 – 34.0)
Medications	
Immunosuppressants, ^b n (%)	182 (47.0)
Hydroxychloroquine, n (%)	167 (43.1)
CCB, n (%)	222 (57.4)
Proton pump inhibitors, n (%)	285 (73.6)
Prokinetics, n (%)	56 (13.4)
Probiotics, n (%)	69 (17.8)
Benzodiazepines, n (%)	38 (9.8)
Antidepressant drugs, n (%)	61 (15.7)
Comorbidities	
Hypertension, n (%)	89 (23.0)
Hypercholesterolemia, n (%)	66 (17.1)
Diabetes mellitus, n (%)	14 (3.6)
Inflammatory bowel disease, n (%)	14 (3.6)

*ACA anticentromere antibodies; ATA antitopoisomerase I antibodies; CCB calcium-channel blockers; CTD connective tissue disease; DLCO diffusing capacity of the lungs for carbon monoxide; FVC forced vital capacity; HRCT high resolution computed tomography; IQR, interquartile range; PASP pulmonary artery systolic pressure; RHC right heart catheterization; SSc, systemic sclerosis.

^aFrom the first non-Raynaud phenomenon symptom.

^bOngoing therapy with methotrexate (66), mycophenolate mofetil (102), azathioprine (10), tocilizumab (4), or exposure in the last 12 months to rituximab (12) or cyclophosphamide (16).

7.5 \pm 1.9, indicative of moderate adherence, without a specific relationship with the geographical origin (MEDAS mean score \pm SD: NI 7.3 \pm 2.1, CI 7.8 \pm 1.8, SI 7.5 \pm 1.8, $P = 0.27$ NI vs. CI, $P = 0.63$ CI vs. SI, $P = 0.90$ NI vs. SI) and body mass index values ($r = 0.015$, $P = 0.871$). No significant associations emerged in univariate analysis between MD adherence and the other considered demographic, clinical, and disease-specific characteristics. The distribution of SSc clinical features and medications according to MD adherence is reported in Supplementary Table 1.

Patients reported outcomes. According to UCLA SCTC GIT 2.0,²⁹ 55 patients (14.2 %) had severe, 70 (18.1%) had moderate, and 242 patients (62.5%) had mild GI symptoms. The median UCLA SCTC GIT 2.0 and Reflux Disease Questionnaire scores for each subitem according to adherence to the MD are reported in Table 2.

Based on HADS scores, 65 patients (16.7 %) were at risk of depression and 91 (23.5%) of anxiety disorder. A total of 71 patients (18.3 %) reported a loss of working hours related to their health status and 77 (19.9%) had a limitation in work (any grade) related to their health status. Health assessment questionnaire (HAQ) values greater than 1.0 were registered for 55 (14.2%) patients, indicating moderate to severe disability. Mean and median values according to adherence to the MD for the subitems of the above instruments are reported in Table 2.

Patients with poor adherence to the MD, compared with those with optimal adherence, showed higher mean scores in HADS depression ($P = 0.048$), HAQ ($P = 0.04$), Raynaud phenomenon SHAQ visual analog scale (VAS) ($P = 0.03$), digital ulcer SHAQ VAS ($P < 0.001$), and perceived limitation because of the disease SHAQ VAS ($P = 0.05$). Poor adherence to the MD was associated with a higher derived percentage of time missed at work ($P = 0.05$).

Adherence to the MD (14-MEDAS score) was inversely correlated to the HADS depression score ($r = -0.232$, $P = 0.003$) (Figure 1A), HADS anxiety score ($r = -0.181$, $P = 0.040$), and severity of Raynaud phenomenon evaluated at SHAQ ($r = -0.220$, $P < 0.001$) and derived percentage of work impairment ($r = -0.323$, $P = 0.030$). Among GI symptoms, we noted an inverse correlation between the 14-MEDAS score and UCLA SCTC GIT 2.0 reflux item score ($r = -0.160$, $P = 0.037$) (Figure 1B).

DISCUSSION

Our survey showed that the general level of adherence to the MD according to a widely used screener is moderate in a large cohort of unselected patients with SSc in Italy. Only 17.3% of patients showed optimal adherence to the MD without remarkable geographical variations.

Recently, a number of studies have assessed adherence to the MD using screening tools in the Italian general population. QueMD, an instrument similar to 14-MEDAS,^{30,31} also showed moderate MD adherence levels. García-Conesa and colleagues reported in their 14-MEDAS validation study²³ a mean score of 6.9 ± 1.6 for the Italian cohort. This value is still classified as

Table 2. Items differences in patients' reported outcomes according to MD adherence*

	Low adherence (n = 54)	Medium adherence (n = 276)	High adherence (n = 57)	P
UCLA SCTC GIT 2.0				
Reflux, median (IQR)	0.36 (0.25–0.63)	0.35 (0.13–0.75)	0.35 (0.00–0.63)	0.628
Distension/bloating, median (IQR)	0.75 (0.25–1.00)	0.75 (0.25–1.25)	0.75 (0.25–1.00)	0.864
Diarrhea, median (IQR)	0.00 (0.00–0.00)	0.00 (0.00–0.50)	0.00 (0.00–0.50)	0.287
Constipation, median (IQR)	0.38 (0.00–0.50)	0.250 (0.00–0.75)	0.250 (0.00–0.38)	0.959
Social functioning, median (IQR)	0.00 (0.00–0.62)	0.16 (0.00–0.50)	0.16 (0.00–0.50)	0.105
Emotional well being, median (IQR)	0.00 (0.00–0.22)	0.11 (0.00–0.44)	0.00 (0.00–0.11)	0.562
RDQ				
Heartburn, median (IQR)	0.00 (0.00–0.50)	0.25 (0.00–1.25)	0.00 (0.00–1.25)	0.423
Regurgitation, median (IQR)	0.50 (0.00–1.00)	0.25 (0.00–1.25)	0.25 (0.00–1.25)	0.924
Dyspepsia, median (IQR)	0.63 (0.00–2.00)	0.50 (0.00–1.50)	0.50 (0.00–1.50)	0.120
GERD, median (IQR)	0.31 (0.00–0.78)	0.50 (0.00–1.00)	0.50 (0.00–1.19)	0.685
HADS				
Depression, mean \pm SD	8.8 \pm 4.7	6.3 \pm 3.7	5.7 \pm 3.5	0.734
Anxiety, mean \pm SD	7.4 \pm 4.4	8.3 \pm 4.5	7.3 \pm 4.6	0.819
WPAI				
Work time missed, %, median (IQR)	0.0 (0.0–17.0)	0.0 (0.0–0.0)	0.0 (0.0–3.8)	0.380
Work impairment, %, median (IQR)	30.0 (5.0–60.0)	0.0 (10.0–30.0)	0.0 (0.0–22.5)	0.260
Scleroderma-HAQ				
Pain, VAS, median (IQR)	20.0 (5.0–50.0)	15.00 (0.0–40.0)	15.0 (0.0–40.0)	0.356
Raynaud, VAS, median (IQR)	22.5 (0.0–36.3)	20.00 (5.0–40.0)	20.0 (5.0–40.0)	0.591
Ulcers, VAS, median (IQR)	0.0 (0.0–30.0)	0.00 (0.0–10.0)	0.0 (0.0–5.0)	0.730
Breathing, VAS, median (IQR)	5.0 (0.0–35.0)	5.00 (0.0–28.8)	0.0 (0.0–5.0)	0.717
Limitation, VAS, median (IQR)	35.0 (5.0–55.0)	30.00 (11.3–53.8)	10.0 (0.0–40.0)	0.196
HAQ, median (IQR)	0.38 (0.00–0.75)	0.25 (0.00–0.88)	0.00 (0.00–0.75)	0.548

*Source: According to UCLA SCTC GIT 2.0, at least moderate GI involvement is defined by a score greater than or equal to 1.0 for distension and bloating and by a score greater than or equal to 0.5 for all the other items (29). GERD, gastroesophageal reflux disease; HADS, Hospital Anxiety and Depression Scale; HAQ, health assessment questionnaire; IQR, interquartile range; RDQ, Reflux Disease Questionnaire; UCLA SCTC GIT, University of California at Los Angeles Scleroderma Clinical Trial Consortium Gastrointestinal Tract; VAS, visual analog scale; WPAI, Work Productivity and Activity Impairment Questionnaire.

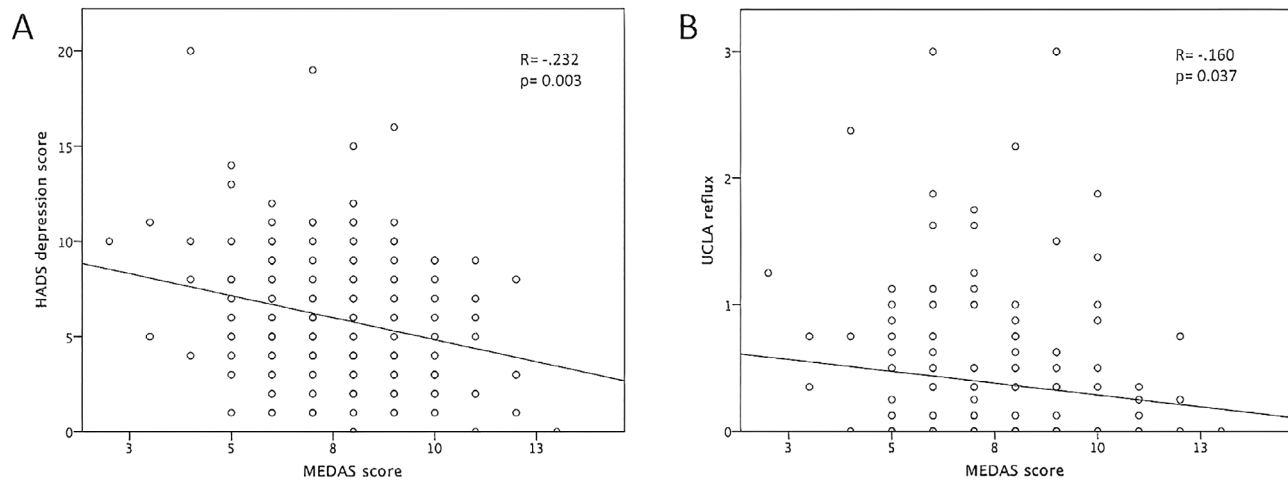


Figure 1. Correlation between adherence to the Mediterranean diet (MEDAS) and **(A)** depression (HADS) and **(B)** reflux (UCLA SCTC GIT 2.0). HADS, Hospital Anxiety and Depression Scale; MEDAS, Mediterranean Diet Adherence Screener; UCLA, University of California at Los Angeles.

indicative of moderate adherence to MD but is lower than our cohort's. Significant demographic differences between the two cohorts should be considered, which could partially account for this difference, particularly with regard to mean age and the percentage of female subjects, which are both higher in our cohort. Using a web-based Medi-Lite score, Dinu and colleagues found that female gender and age greater than 45 years were associated with a higher probability of being adherent to MD.³² Notably, MD drop-out in Italy, specifically in the younger population, is a matter of interest and is currently being assessed to inform public health actions.³³

In univariate analysis, we noted some specific associations between MD adherence, mood, and QoL. In particular, poor adherence to MD was associated with more prominent depressive mood aspects. The same patients reported a major impact on their work activities in terms of time missed, whereas the perceived severity of Raynaud phenomenon, digital ulcers, and reflux that heavily affect the QoL were milder in the case of optimal adherence to the MD.

Although exploring a causal link between a nutritional pattern and disease severity and comorbidity is beyond the scope of the present study, these results do not disagree with the hypothesis that an optimal adherence to MD may be related to better health outcomes.

The relationship between MD, cognitive function, and mood has already been investigated, in which larger population studies and clinical trials suggest a protective role of MD against depression.^{34,35} A possible association between depression and anxiety and nutritional impairment has been previously reported in SSc, presuming an influence of mood on reduced appetite and motivation for key nutritional tasks such as food purchasing and preparation.³⁶ We cannot rule out the possibility that similar mechanisms may have partly contributed to what we observed in our population.

Regarding GI symptoms, it has been suggested that a MD pattern may be effective in controlling gastroesophageal reflux symptoms.^{37,38}

Overall, it is interesting to note that the pleiotropic biological effects attributed to MD intersect with several aspects of SSc pathogenesis, including inflammation,³⁹ endothelial dysfunction,⁴⁰ and microbiota modulation.⁴¹ These aspects might be worthy of further investigation through translational research approaches useful in elucidating any underlying mechanistic links.

Some limitations are to be considered in interpreting the results of this study. First, the present study's cross-sectional design and statistical approach, based on univariate analysis, are inadequate for exploring a causal relationship between eating habits, mood, and QoL. This relationship is likely to be complex and bidirectional. In the specific case of scleroderma, for example, it cannot be ruled out that disease-specific features, such as the presence of digital ulcers or reflux symptoms, may influence the patient's food preparation and choice, leading to a shift from a MD pattern. Adequately powered prospective studies could help elucidate these issues in the future.

Second, no FFQs or food diaries were administered in this study to assess concordance and validate the 14-MEDAS in this specific population. However, the validity of this tool has been addressed in several specific studies. García-Conesa and colleagues conducted the most comprehensive validation study to date, showing a moderate association with a classic 3-day food diary.²³ Other similarly designed studies have investigated the validity of 14-MEDAS in individual populations showing fair-to-moderate association levels.^{42–45} These data support its potential applicability to comparatively differentiate MD adherence between populations from different geographical areas.

The 14-MEDAS cut-offs for determining MD adherence levels in our study are those suggested by the authors of the

instrument²² and were used for comparison of baseline characteristics of the PREDIMED trial study population, highlighting a different distribution of different metabolic parameters and cardiovascular disease across three adherence categories. However, it should be kept in mind that different cut-offs not analyzed in our study have been used for 14-MEDAS in other settings and depending on the outcomes analyzed. In general, it is acknowledged that further efforts are needed to improve standard validation protocols to measure MD adherence.

In conclusion, the MD is recognized as a dietary pattern of interest for human health with postulated biological effects intersecting SSc physiopathology. Given the paucity of therapeutic solutions for SSc, an approach that integrates the adoption of a nutritional intervention based on MD is worthy of further investigation through translational and clinical research. To our knowledge, this is the first report on MD in a scleroderma population, and we believe it may be helpful to inform future initiatives to study the nutrition of patients with SSc. Administration of the 14-MEDAS was feasible regarding the time required for patient completion and acceptance in the context of scheduled follow-up visits in the setting of scleroderma specialty clinics. If robustly validated in the SSc population, it could be a reasonable choice to assess adherence to the MD pattern in future studies.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. De Luca had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. De Luca.

Acquisition of data. Natalello, Abignano, Ferlito, Temiz Karadağ.

Analysis and interpretation of data. Natalello, Campochiaro.

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