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Original article

Beneficial effect of Mediterranean diet on disease activity and cardiovascular risk in systemic lupus erythematosus patients: a cross-sectional study

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Abstract

Objective. To analyse the influence of the Mediterranean diet (Med Diet) on SLE activity, damage accrual and cardiovascular disease risk markers.

Methods. A cross-sectional study was conducted on 280 patients with SLE [46.9 (12.85) years]. Med Diet adherence was assessed through a 14-item questionnaire on food consumption frequency and habits (total score from 0 to 14 points; higher score is greater adherence to the Med Diet). CRP, homocysteine, SLEDAI-2K (SLE disease activity), and SLICC/ACR and SDI (damage accrual) were measured. Obesity, diabetes mellitus, hypertension and blood lipids, among others, were considered cardiovascular disease risk factors.

Results. Greater adherence to the Med Diet was significantly associated with better anthropometric profiles, fewer cardiovascular disease risk factors, and lower disease activity and damage accrual scores ($P \leq 0.001$ for SLEDAI and SDI). An inverse relationship between the Med Diet score and SLEDAI ($P \geq 0.001$; $\beta = -0.380$), SDI ($P \leq 0.001$; $\beta = -0.740$) and hsCRP ($P = 0.039$; $\beta = -0.055$) was observed. The odds ratio for having active SLE (SLEDAI ≥ 5) or the presence of damage (SDI ≥ 1) was lower among patients whose Med Diet score was higher ($P \leq 0.001$). Finally, greater consumption of Med Diet foods (olive oil, fruits, vegetables, fish, etc.) and abstaining from red meat and meat products, sugars and pastries was associated with less SLE clinical activity and damage.

Conclusion. Greater adherence to the Med Diet seems to exert a beneficial effect on disease activity and cardiovascular risk in SLE patients. To confirm these findings, further longitudinal studies would be of interest.

Key words: autoimmune, lupus, Mediterranean diet, inflammation, cardiovascular disease, atherosclerosis, systemic lupus erythematosus

CLINICAL SCIENCE

Introduction

The Mediterranean diet (Med Diet) is a traditional dietary pattern based on whole or minimally processed foods and a high intake of vegetables, fruits, whole grains, fish and olive oil, with moderate consumption of red meat and wine [1].

Numerous studies have linked a high-quality dietary pattern such as the Med Diet with a lower incidence of chronic and inflammatory diseases [2], including cardiovascular disease (CVD) [3], metabolic syndrome [4], obesity [5, 6], diabetes [7] and cancer [8], in addition to a better prognosis. Additionally, a few recent studies have reported that the Med Diet positively impacts autoimmune diseases [9, 10]. In RA, Med Diet interventions modulated inflammatory activity, increased physical function and improved vitality [10]. Similarly, adherence to the Med Diet may decrease the risk of other autoimmune diseases, including multiple sclerosis (MS) [9]. However, the usefulness of the Med Diet as a high-quality dietary pattern for other autoimmune diseases has not yet been investigated.

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Rheumatology key messages

- Greater adherence to the Mediterranean diet positively impacts SLE disease activity, damage accrual and cardiovascular risk.
- Anti-inflammatory diets may induce changes in inflammatory and cardiovascular risk markers that could benefit SLE prognosis.
- SLE patients would benefit from nutritional education programmes focused on maintaining anti-inflammatory dietary patterns.

SLE is one of the most representative autoimmune diseases [11]. Patients with SLE have a higher risk of developing CVD, the main cause of morbidity and mortality [12, 13]. The increased CVD risk in lupus patients is likely to be multifactorial, resulting from both SLE-specific risk factors such as disease severity or drug therapy, and traditional cardiovascular risk factors, such as obesity, hypertension and dyslipidaemia, among others [14]. In addition, inflammation processes in SLE promote the development of atherosclerosis, endothelial damage and SLE progression, contributing to CVD risk [15].

Previous research has shown that dietary factors can modulate inflammation and CVD risk [16, 17] and may play a role in atherogenic processes in SLE [18]. In this context, following a Med Diet is related to improved inflammatory biomarker profiles and lower endothelial cell dysfunction [19]. Similarly, the Med Diet exerts a protective effect against CVD [3], mainly because of small favourable changes in CVD risk factors, including improved blood lipids, blood pressure, blood glucose and waist circumference [20].

Considering the beneficial effects of the Med Diet on inflammatory and autoimmune diseases, and that the role of this healthy dietary pattern has not yet been investigated in SLE, we aimed to analyse the relationship between Med Diet adherence and SLE clinical outcomes.

Methods

Study design and study population

A cross-sectional study was conducted on a population of patients diagnosed with SLE who attended the Systemic Autoimmune Diseases Unit outpatient clinics at one of three public hospitals in the Andalusia region of Spain. All patients met the revised criteria of the ACR or the SLICC criteria for SLE diagnosis [21]. The participants were diagnosed with SLE at least 1 year prior to the start of the study, and were clinically stable with no changes in their Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) [22] score or their medical treatment over the 6-month period prior to the study. We excluded patients with serum creatinine levels $\geq$1.5 mg/dl, cerebrovascular disease, ischaemic heart disease, active infections, major trauma or surgery in the preceding 6 months, pregnancy, or other chronic and/or autoimmune systemic conditions not related to the main disease.

A total of 350 patients with SLE, between 18 and 80 years old, were consecutively approached about participating in this study and were screened for eligibility. After medical consultation, 61 patients were deemed ineligible (26 were excluded for having active infections at the time of the study, 21 had other autoimmune conditions, eight had severe lupus nephritis and six were pregnant) and nine patients declined to participate. Finally, a total of 280 individuals were included in the study after providing written informed consent. Their clinical manifestations, medical records and current medical treatment with antimalarials, immunosuppressors, statins and corticoid therapy (current use and dose) were also recorded. The study was approved by the local ethics committee and the work was conducted in accordance with the standards set out in the Declaration of Helsinki.

Disease activity index and damage index assessments

Disease activity was assessed with the SLEDAI-2K [22]. The SLE Disease Activity Index (SLEDAI) is a list of 24 items, 16 of which are clinical and eight are laboratory results. Meaningful improvement is best defined as a SLEDAI-2K score reduction of 4 points [23].

Disease-related organ damage was assessed using the SLICC/ACR Damage Index (SDI) [24], which was developed to assess irreversible damage in SLE patients, independently of the cause [25].

Anti-double stranded DNA and complement level assays

Anti-double stranded DNA (anti-dsDNA) titres were measured using the commercially available BioPlex 2200 System (Bio-Rad, Hercules, CA, USA). The results are expressed in IU/ml and the cut-off values established by the manufacturer are 5–9 IU/ml (indeterminate) and $\geq$10 IU/ml (positive). Human complement components C3 and C4 were determined quantitatively in serum samples through immunoturbidimetric assays (Beckman Coulter AU System CRP Latex reagent; Beckman Coulter, Brea, CA, USA).

High-sensitivity C-reactive protein and homocysteine determinations

Immunoturbidimetric assays (Beckman Coulter AU System CRP Latex reagent) were used to determine high-sensitivity CRP (hsCRP) levels. According to the American Heart Association guidelines, hsCRP levels below 3.0 mg/l present a low to normal/average cardiovascular risk and individuals with levels in excess of 3.0 mg/l have a high risk of CVD [26].

Homocysteine (Hcy) serum levels were measured with an enzymatic colorimetric assay using Liquid Stable 2-part Homocysteine Reagent (Axis-Shield Diagnostics Ltd, Dundee, UK). Normal laboratory reference levels range between 5–15 μmol/l; however, the recommended ideal level is ≤10 μmol/l in individuals with an increased risk of CVD, such as SLE patients [27].

Cardiovascular risk factors

Comorbidities

The presence of type II diabetes, hypertension and/or dyslipidaemia were considered cardiovascular risk factors.

Blood lipid profile

Venous blood samples were collected between 7:30 and 10:00 a.m. following an overnight fast. Serum samples were analysed immediately using standard laboratory methods to determine the total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides (TG) and biochemical variables used here as cardiovascular risk factors.

Cut-off values for blood lipids were established according to the Guidelines for Dyslipidaemia Treatment: Adult Treatment Panel III (ATP-III). The National Cholesterol Education Programme (NCEP) [28] describes the following cut-off values: total cholesterol <200 mg/dl, high-density lipoprotein cholesterol 40–60 mg/dl, low-density lipoprotein cholesterol <100 mg/dl and TG <150 mg/dl.

Ankle–brachial index and blood pressure

The ankle–brachial index was measured, according to the American Heart Association recommendations, to assess the presence of subclinical atherosclerosis [29, 30]. Systolic blood pressure was measured at ankle level and in the brachial arteries of both arms and legs, using a manual sphygmomanometer (Riester 1312 minimus II, Jungingen, Germany) and a portable vascular Doppler (Hadeco Minidop ES-100VX, Kawasaki, Japan). Blood pressure was measured using a Dinamap vital sign monitor (Model BP 8800, Critikon, Inc., Tampa, FL, USA), following the European Heart Society recommendations.

Mediterranean diet adherence and nutritional data

An in-person interview with each participant was conducted by the same trained nutritionist/dietitian, and the previously validated 14-item Mediterranean Diet Adherence questionnaire, designed and validated by the PREvención con DIeta MEDiterránea group (PREDIMED), was administered [31, 32]. This questionnaire comprises 12 items relating to food consumption frequency plus two on consumption habits with regard to foods considered characteristic of the Med Diet pattern, over the past 6 months. Each question is scored either 0 or 1 and the total score ranges from 0 to 14 points; the higher the score, the greater the adherence to the Med Diet. The questionnaire was performed with 1 point given for each of the following: (i) using olive oil as the main source of culinary fat; (ii) consumption of four or more tablespoons of olive oil per day; (iii) consumption of two or more servings of vegetables per day; (iv) consumption of three or more pieces of fruit per day; (v) consumption of less than one serving (one serving = 100 g) of red meat or hamburger or sausages per day; (vi) consumption of less than one serving of animal dairy and fats such as butter, margarine, or cream per day; (vii) consumption of less than one glass of sweetened beverages per day; (viii) consumption of seven or more glasses (100 ml) of red wine per week; (ix) consumption of three or more servings (one serving = 150 g) of pulses per week; (x) consumption of three or more servings (one serving = 150 g) of fish per week; (xi) consumption of fewer than two commercial pastries and/or commercial sweets per week; (xii) consumption of three or more servings (one serving = 30 g) of tree nuts per week; (xiii) preferring white meat over red meat; and (xiv) consumption of *sofrito* (a sauce made with tomato, garlic, onions and peppers sautéed in olive oil) two or more times per week.

In addition, a 24-h diet recall was used to estimate food consumption. Patients were asked about the portions and amounts of each food or beverage item they had consumed, the number and amount of ingredients used in each recipe, meal preparation, consumption of sugary foods, alcoholic and non-alcoholic drinks, and added sugar in the preceding 24 h. The food and beverage intake reported was converted into nutrient, total energy, and alcohol intake information using El Alimentador software (Fundación Alimentación Saludable, Madrid, Spain) [33].

Anthropometric assessment

A body composition analyser (TANITA BC-418MA Tokyo, Japan) was used to measure body weight (kg) and fat mass percentage to the nearest 0.1 kg. Height (m) was measured using a Seca 763 measuring station (Seca, Hanover, MD, USA). All the measurements were performed twice, with the participants wearing light indoor clothing and without shoes. The patients' BMIs were calculated by dividing their body weight (kg) by the square of their height (m^2) and this was classified according to the World Health Organization guidelines [34].

Statistical analysis

SPSS Statistics version 21.0 (IBM Corp., Armonk, NY, USA) was used for all the analyses. The Med Diet

adherence score was classified as follows: low adherence ($\leq$5 points); medium adherence 6–9 points; and good adherence $\geq$10 points, according to a previous PREDIMED report [5]. We compared the baseline characteristics of the participants according to these three adherence categories (means and S.D. or number and percentage for each variable). Significance of differences between these was tested using one-way ANOVA for continuous variables and the chi-square test for categorical variables. Linear regression analyses were also used to examine the relationship between the Med Diet score, clinical disease variables and inflammatory markers. Multivariable linear regression modelling was used to estimate differences in clinical disease variables and inflammatory markers, with adherence to the Med Diet as the continuous variable. Age, sex, medical treatment (immunosuppressors, corticoids or antimalarials), smoking status and BMI were included in all the analyses as confounding factors using a stepwise algorithm (forward method).

In all the analyses, the SLEDAI, SDI, anti-dsDNA, complement C3 and C4, hsCRP, Hcy, and fibrinogen data were adjusted for age, sex, medical treatment (immunosuppressants, corticoids, and antimalarials), smoking status and BMI. Multivariable logistic regression analyses were also used to estimate the odds ratios (OR) for active SLE (SLEDAI $\geq$5), damage (SDI $\geq$1) and elevated cardiovascular risk (hsCRP $>$3) for participants with greater adherence to the Med Diet (6–10 points) *vs* those with poorer adherence ($\leq$5 points, the reference category) in separate models—one unadjusted and the other after adjusting for the aforementioned confounding factors; P values <0.05 were considered statistically significant.

Results

The mean age of the study participants was 46.9 (12.85) years and the majority (90.4%) were female. The main characteristics of the participants according to their Med Diet adherence category are shown in Table 1. Most participants had a medium (43.2%) or high (51.1%) adherence to the Med Diet, and there were significant differences in the study variables according to these adherence categories. Firstly, participants with high Med Diet adherence had better anthropometric data profiles, including lower BMI and fat mass percentage, compared with the medium and low adherence categories ($P = 0.001$ and $P = 0.002$, respectively). In terms of CVD risk factors, obesity was significantly linked to Med Diet adherence ($P = 0.026$): patients with very low adherence ($\leq$5 points) had the highest percentage of obesity (37.5%). There were also significant differences in the TG ($P = 0.003$), Hcy ($P = 0.021$) and albumin ($P = 0.042$) laboratory parameters and Med Diet adherence categories (Table 1). Interestingly, the association with TG was also evidenced when Med Diet adherence was analysed according to the cut-offs for dyslipidaemia ($P = 0.001$, Table 1). No associations were found for the remaining CVD risk variables investigated, including the ankle–brachial index. Interestingly, as shown in Table 1, compared with the medium and high adherence groups, 62.5% of the patient group with the poorest adherence to the Med Diet used corticoids ($P = 0.0017$) and at a higher dose ($P = 0.002$).

There were also significant differences in SLE activity and damage according to Med Diet adherence (SLEDAI: $P \leq 0.001$; SDI: $P \leq 0.001$; Table 1). However, except for discoid rash, no significant associations were found between Med Diet adherence and the different SLE clinical manifestations (Table 1). Similarly, the linear regression analyses revealed inverse relationships between Med Diet score and SLEDAI ($P \geq 0.001$; $\beta = -0.380$, 95% CI: -0.464, -0.296); SDI ($P \leq 0.001$; $\beta = -0.740$, 95% CI: -0.938, -0.542); and hsCRP ($P = 0.039$; $\beta = -0.055$, 95% CI: -0.108, -0.003) after adjusting for age, sex, smoking status, medical treatments and BMI (Table 2). When the clinical manifestations were considered independently, no significant associations were observed.

To further investigate the relationship between the Med Diet and SLE clinical parameters, we tested multiple logistic regression models with polynomial contrasts. An inverse association between adherence to the Med Diet and the risk of having active SLE (SLEDAI $\geq$5) or the presence of damage (SDI $\geq$1) was demonstrated ($P \leq 0.001$ in both cases; Table 3); these associations persisted after adjusting for confounding factors (age, sex, smoking status, medical treatment and BMI). The SLE patients with the highest Med Diet adherence scores ($\geq$10 points) had the lowest OR for active SLE (SLEDAI $\geq$5) and the presence of damage (SDI $\geq$1) in both unadjusted (OR: 0.06; 95% CI: 0.20, -1.71; and OR: 0.05; 95% CI: 0.006, -0.36, respectively) and adjusted models (OR: 0.13; 95% CI: 0.04, -0.50; and OR: 0.04; 95% CI: 0.005, –0.352, respectively), as illustrated in Table 3. No significant interactions were found between hsCRP levels and the risk of having active SLE or damage.

Finally, the consumption of specific Med Diet items was analysed according to the presence of active SLE or damage (Table 4). As can be observed, significant differences were observed for several items, with lower consumption of olive oil, vegetables, fruit, legumes, fish, nuts and *sofrito* per day seen among patients with active SLE or higher damage scores (Table 4). Conversely, these patients reported a greater consumption of red meat or meat product, in addition to commercial sugary foods and pastries.

Discussion

This study assessed, for the first time, the association between adherence to the Med Diet and SLE activity, damage accrual and CVD risk markers in a well-characterized population of patients with SLE. Our results revealed that SLE patients with higher Med Diet adherence scores had better anthropometric profiles and serum levels of cardiovascular risk and/or inflammatory markers, including hsCRP, Hcy, TG and albumin.

Table 1 Baseline and clinical characteristics of SLE patients according to scores of Med Diet adherence

Characteristic	≤5 points	6–9 points	≥10 points	*P*
n (%)	16 (5.71)	121 (43.21)	143 (51.1)	
Females, *n* (%)	16 (100)	11 (90.90)	127 (88.81)	0.343
Age, mean (S.D.), years	38.63 (9.75)	46.33 (13.470	28.29 (12.86)	0.14
Anthropometric data and energy intake				
Weight, mean (S.D.), kg	71.72 (26.46)	69.37 (14.65)	68.01 (14.97)	0.585
Height, mean (S.D.), m	1.57 (0.06)	1.61 (0.07)	1.62 (0.08)	**0.043**
BMI, mean (S.D.), kg/m^2	31.45 (7.91)	26.44 (4.78)	25.90 (5.44)	**0.001**
Fat mass, mean (S.D.), %	38.54 (7.85)	34.96 (8.15)	32.84 (9.01)	**0.002**
Total energy intake, mean (S.D.), kcal/day	1921.43 (578.55)	1848.45 (513.33)	1704.96 (486.23)	**0.037**
Cardiovascular risk factors				
Hypertension, *n* (%)	5 (31.25)	37 (30.58)	44 (30.76)	0.998
Diabetes, *n* (%)	1 (6.25)	5 (4.13)	4 (2.79)	0.707
Obesity, *n* (%)	6 (37.5)	25 (20.66)	29 (20.27)	**0.026**
Dyslipidaemia, *n* (%)	7 (43.75)	42 (34.71)	51 (35.6)	0.788
TC, mean (S.D.), mg/dl	183.33 (35.55)	185.55 (41.24)	183.41 (44.95)	0.918
TC (high), *n* (%)	4 (25)	43 (36.13)	46 (32.17)	0.605
TG, mean (S.D.), mg/dl	128.29 (49.80)	108.80 (58.43)	91.64 (43.90)	**0.003**
TG (high), *n* (%)	6 (37.5)	15 (12.7)	10 (7)	**0.001**
HDL-C, mean (S.D.), mg/dl	54.60 (17.70)	56.54 (14.26)	59.10 (17.07)	0.314
HDL-C (low), *n* (%)	4 (25)	14 (11.7)	11 (7.74)	0.085
LDL-C, mean (S.D.), mg/dl	103.44 (38.23)	108.87 (33.56)	107.59 (33.59)	0.823
LDL-C (high), *n* (%)	9 (56.25)	68 (57.14)	79 (55.24)	0.954
SBP, mean (S.D.), mmHg	115.40 (14.89)	122.54 (18.13)	118.74 (19.35)	0.485
DBP, mean (S.D.), mmHg	83.2 (11.63)	81.54 (10.11)	85.75 (22.25)	0.471
ABI, mean (S.D.)	0.98 (0.15)	1.01 (0.13)	1.01 (0.12)	0.760
Clinical data				
SLE duration, mean (S.D.), years	8.75 (7.09)	9.62 (7.06)	8.61 (6.17)	0.352
Number of complications	3.5 (0.97)	3.58 (1.39)	3.20 (1.31)	0.201
SLEDAI score[a], mean (S.D.)	5.25 (2.75)	3.79 (2.87)	1.44 (1.78)	**<0.001**
SDI score[a], mean (S.D.)	2.06 (2.14)	1.31 (1.33)	0.56 (0.78)	**<0.001**
hsCRP[a], mean (S.D.), mg/dl	3.95 (4.73)	3.92 (6.29)	2.38 (2.85)	0.089
Hcy[a], mean (S.D.), μmol/l	12.95 (4.31)	13.81 (10.14)	11.30 (4.02)	**0.021**
Anti-dsDNA[a], mean (S.D.), IU/ml	21.24 (27.55)	21.92 (38.17)	14.82 (36.44)	0.628
Complement C3 level[a], mean (S.D.), mg/dl	123.59 (36.94)	107.55 (27.30)	108.34 (27.61)	0.248
Complement C4 level[a], mean (S.D.), mg/dl	23.43 (9.33)	20.93 (13.90)	24.27 (19.59)	0.519
WBC count, mean (S.D.), ×1000/μl	6010.43 (3162.83)	5784.89 (2287.03)	5623.30 (2070.90)	0.841
Platelet count, mean (S.D.), ×1000/μl	247062 (94095)	232585 (76841)	220955 (63854)	0.431
ESR, mean (S.D.), mm/h	23.75 (19.57)	20.05 (16.95)	17.44 (13.30)	0.325
Hb level, mean (S.D.), g/dl	13.23 (1.28)	13.27 (1.29)	14.53 (9.31)	0.344
Albumin, mean (S.D.), g/dl	3.81 (0.36)	4.03 (0.38)	4.15 (0.37)	**0.042**
Fibrinogen[a], mean (S.D.), mg/dl	345.32 (66.64)	348.59 (82.02)	339.78 (85.56)	0.916
SLE Clinical manifestations				
Nephritis, *n* (%)	5 (31.25)	29 (25.66)	33 (23.91)	0.801
Serositis, *n* (%)	2 (12.5)	9 (8)	21 (15.22)	0.212
Arthritis, *n* (%)	7 (43.75)	66 (58.4)	76 (55.07)	0.526
Oral ulcers, *n* (%)	8 (50)	63 (55.75)	67 (48.55)	0.520
Malar rash, *n* (%)	10 (62.5)	64 (56.63)	71 (51.44)	0.567
Discoid rash, *n* (%)	1 (6.25)	24 (21.23)	10 (7.24)	**0.003**
CNS, *n* (%)	1 (6.25)	18 (15.93)	15 (10.9)	0.354
Thrombocytopenia, *n* (%)	3 (18.75)	20 (17.7)	18 (13.04)	0.552
Lymphopenia, *n* (%)	9 (56.25)	76 (67.25)	77 (55.8)	0.169
Haemolytic anaemia, *n* (%)	1 (6.25)	10 (8.85)	8 (5.79)	0.639
Medication used				
Antimalarial use, *n* (%)	14 (87.5)	89 (74.16)	119 (84.04)	0.139
Immunosuppressor use, *n* (%)	7 (43.75)	54 (45)	43 (30.06)	0.087
Corticoid use, *n* (%)	10 (62.5)	51 (42.5)	49 (34.26)	**0.017**

[a]Adjusted by age, sex, medical treatment (immunosuppressor, corticoid and antimalarial use), smoking status and BMI. *P*-value determined by one-way ANOVA (continuous variables) or chi square test (categorical variables). Values in bold are considered statistically significant. ABI: ankle brachial index; anti-dsDNA: anti-double stranded DNA antibodies; DBP: diastolic blood pressure; Hb: haemoglobin; Hcy: homocysteine; HDL-C: high density lipoprotein cholesterol; hsCRP: high-sensitivity CRP; LDL-C: low density lipoprotein cholesterol; SBP: systolic blood pressure; SDI: damage index for systemic lupus erythematosus; SLEDAI: systemic lupus erythematosus disease activity index; TC: total cholesterol; TG: triglycerides; WBC: white blood cells.

Table 2 Relationship between clinical disease variables and inflammatory markers and Med Diet

Clinical parameter	Mediterranean diet adherence (continuous)	
	β (95% CI)	*P*
SLE duration (years)	−0.025 (−0.063, 0.014)	0.208
Number of complications	0.367 (−0.105, 0.840)	0.127
SLEDAI score	−0.380 (−0.464, −0.296)	**<0.001**
SDI score	−0.740 (−0.938, −0.542)	**<0.001**
hsCRP (mg/dl)	−0.055 (−0.108, −0.003)	**0.039**
Hcy (μmol/l)	−0.033 (−0.071, 0.006)	0.093
Anti-dsDNA (IU/ml)	−0.002 (−0.009, 0.005)	0.553
Complement C3 level (mg/dl)	−0.006 (−0.015, 0.004)	0.251
Complement C4 level (mg/dl)	0.011 (−0.004, 0.026)	0.139

Data were adjusted by age, sex, medical treatment (immunosuppressor, corticoid and antimalarial use), smoking status and BMI. *P*-values in bold are considered statistically significant. Anti-dsDNA: anti-double stranded DNA antibodies; Hcy: homocysteine; hsCRP: high-sensitivity CRP; SDI: damage index for systemic lupus erythematosus; SLEDAI: systemic lupus erythematosus disease activity index.

Table 3 Association between Med Diet and the risk of having active SLE or damage presence

Active SLE and damage presence	OR (95% CI)			*P*
	≤5 points (ref)	6–9 points	≥10 points	
Active SLE[a] (unadjusted model)	1	0.37 (0.35, 2.98)	0.06 (0.20, 1.71)	**<0.001**
Adjusted OR[b]	1	0.75 (0.22, 2.55)	0.13 (0.04, 0.50)	**<0.001**
Damage presence[c] (unadjusted model)	1	0.11 (0.014, 0.85)	0.05 (0.006, 0.36)	**<0.001**
Adjusted OR[b]	1	0.09 (0.01, 0.87)	0.04 (0.005, 0.352)	**<0.001**
hsCRP >3	1	1.01 (0.35, 2.98)	0.58 (0.20, 1.71)	0.102
Adjusted OR[b]	1	2.21 (0.55, 8.86)	1.41 (0.35, 5.75)	0.230

[a]Active systemic lupus erythematosus, defined by SLEDAI ≥5. [b]Adjusted OR by age, sex, smoking status and medical treatment (immunosuppressor, corticoid and antimalarial use) and BMI. [c]Damage presence was defined by an SDI ≥1. hsCRP: high sensivity CRP; OR: odds ratio; SDI: damage index for systemic lupus erythematosus; SLEDAI: systemic lupus erythematosus disease activity index.

To date, the relationships between the Med Diet and other autoimmune diseases have only been investigated for RA, MS and osteoarthritis. In agreement with our findings for SLE, the Med Diet has been associated with reduced inflammatory disease activity and increased physical function and vitality in RA sufferers [35]. Similarly, a recent systematic review concluded that using the Med Diet to prevent RA could be beneficial [10]. In addition, in a large population of patients with osteoarthritis, greater adherence to the Med Diet was associated with a better quality of life, less pain and disability, and fewer symptoms of depression [36]. It has also been suggested that adherence to the Med Diet may decrease the risk of disease in MS patients [9].

The molecular mechanisms by which the Med Diet exerts these beneficial effects are still poorly understood. Growing evidence suggests that the microbiota plays a role in SLE [37–39]. Indeed, dietary changes are known to affect both the composition and the function of the gut microbial community, which could play a role in the pathogenesis of SLE [37]. The gut microbiota of SLE patients has been associated with an imbalance in the proportions of T helper 17 (Th17) and Treg cells [39], as well as the development of antinuclear antibodies [38]. In addition, the ratio of Firmicutes to Bacteroidetes is reduced in SLE patients, which has been related to several inflammatory diseases [40]. Molecular mimicry and the ability of some proteins to bind to B and T cells activating immune responses may be another mechanism that could play an important role in gut microbes inducing autoimmunity [40]. For these reasons, gut microbiota influenced by dietary changes may play a role in the course of SLE.

The modulation of inflammatory processes may also be an important factor explaining the benefits of the Med Diet in patients with autoimmune diseases [41, 42]. The presence of olive oil, certain nutrients like omega 3, carotenoids and vitamin C, and non-nutritional foods in the Med Diet, could modulate inflammation both acutely and

TABLE 4 Med Diet items according to disease activity and damage accrual categories

Mediterranean diet items	Active lupus (SLEDAI ≥5)	Inactive lupus (SLEDAI ≤5)	*P*	Damage presence (SDI ≥1)	No damage (SDI = 0)	*P*
Using olive oil as main culinary fat, %	91.4	99.5	**<0.001**	96.6	99.2	0.135
≥4 spoons of olive oil per day, %	94.8	98.6	0.081	96.6	99.2	0.306
≥2 servings per day of vegetables, %	17.2	55.4	**<0.001**	34.9	61.8	**<0.001**
≥3 fruit units per day, %	31	49.6	**0.012**	43.0	48.9	0.323
<1 serving per day of red meat, hamburger or meat products, %	72.4	92.3	**<0.001**	84.6	92.4	**0.043**
<1 serving per day of butter, margarine or cream, %	82.8	90.1	0.118	85.9	91.6	0.135
<1 serving per day of sweetened or carbonated beverages, %	72.4	72.8	0.476	70.5	85.5	**0.004**
Moderate wine consumption, %	1.7	9	0.081	5.4	9.9	0.149
≥3 servings of legumes per week, %	43.1	67.1	**0.001**	41.6	66.4	0.167
≥3 servings of fish per week, %	25.9	42.8	**0.019**	36.2	42.7	0.266
<2 times per week of commercial sweets or pastries, %	50	64.9	**0.038**	52.3	72.5	**0.001**
≥3 servings of nuts per week, %	20.7	46.4	**<0.001**	35.6	47.3	**0.046**
Preferring white meat over red meat, %	82.8	95	**0.002**	89.3	96.2	**0.028**
≥2 times per week seasoning dishes with *sofrito*[a]	68.9	87.8	**<0.001**	77.2	91.6	**0.001**

[a]Tomato, pepper and garlic-based sauce. *P*-values in bold are considered statistically significant ($p \leqslant 0.05$). SDI: damage index for systemic lupus erythematosus; SLEDAI: systemic lupus erythematosus disease activity index.

chronically [43]. In this study, we have found that adherence to the Med Diet by SLE patients is linked to reduced levels of certain inflammatory biomarkers, including hsCRP and Hcy, which are related to increased cardiovascular risk [44]. This is in line with previous studies in which the Med Diet, or similar high-quality dietary patterns, has been associated with reduced levels of pro-inflammatory markers in the general population [45], as well as in individuals with inflammatory conditions, such as osteoarthritis [46] or RA [42]. However, adherence to Med Diet was not associated with SLE specific inflammatory markers such as DNA-Abs, C3 or C4 when they were considered independently. Thus, it is possible that SLE activity and accumulated damage measured by SLEDAI and SLICC could be influenced by mechanisms of secondary non-specific inflammatory injury. Further studies would be necessary to investigate this issue.

Another potential benefit of good adherence to the Med Diet for SLE patients could be reduced cardiovascular risk, thanks to the diet's indirect effects on metabolic factors. Our findings reveal a better lipid profile, BMI and fat mass percentage, and a lower prevalence of obesity in patients with high Med Diet adherence scores. In this context, other studies have reported an independent association between obesity and worse SLE disease activity, suggesting that body weight and adiposity may also influence SLE outcomes [47, 48].

On the other hand, our findings reveal that consuming certain components of the Med Diet, such as olive oil, fruits, vegetables, *sofrito*, legumes, fish and nuts, as well as abstaining from red meats, meat products, sugary foods and pastries, is associated with a lower SLEDAI score. Similar results have been described for obesity [5], metabolic syndrome [4] and in relation to hsCRP serum levels [49]. These findings agree with the hypothesis that not all the components of the Med Diet are likely to provide the same level of protection [50]; it appears that olive oil, fruits, vegetables (dietary fibre) and fish are the most protective factors in the Med Diet [51].

Taken together, our preliminary results suggest that adherence to the Med Diet influences disease activity, damage accrual and cardiovascular risk factors in SLE patients. These effects might be mediated through changes in the immune system, inflammatory markers and other CVD risk factors that affect the course and prognosis of SLE. Thus, along with their usual medical treatment, SLE patients would benefit from nutritional counselling and education to help adapt their lifestyles towards the Med Diet pattern. This would help slow the progression of SLE and the damage it causes, and reduce the CVD risks associated with the disease.

This study has certain potential limitations. Firstly, because of its cross-sectional design, no causal conclusions can be drawn. In this context, possible relationships between Med Diet adherence and cumulative doses of medication, especially steroids and immunosuppressive drugs, has not been analysed. Past doses of these drugs could indicate lower disease severity, which may influence the results. Longitudinal studies that gather data over a prolonged period, as well as interventional studies, are therefore necessary to confirm the effect of the Med Diet on SLE. The main strength of this study is that it is the first to assess the impact of an anti-inflammatory dietary pattern like the Med Diet on SLE. Our study comprised a well-

characterized cohort of individuals with SLE, including early-stage patients and excluding those with lupus flare-ups or other associated autoimmune conditions. Another important strength is that we considered the use of medication (including antimalarials, immunosuppressors and corticosteroids), age, sex, smoking status and BMI, which may all influence the results.

In conclusion, greater adherence to the Med Diet positively impacts SLE disease activity, damage accrual and cardiovascular risk, and there is a relationship between this diet pattern and the course of SLE. Considering the high risk of CVD and other comorbidities in SLE, high-quality anti-inflammatory dietary patterns may play a role in disease management. However, further longitudinal studies on SLE patients, including dietary intervention trials, are needed to confirm our preliminary findings.

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