Adherence to the Mediterranean diet and the impact on clinical features in primary Sjögren's syndrome

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ABSTRACT

Objective. *The relationship between dietary patterns, including the Mediterranean diet, and rheumatic and musculoskeletal diseases (RMDs) has been increasingly assessed but data on patients with established primary Sjögren's syndrome (pSS) is lacking. The aim of the study was to explore the adherence to the Mediterranean diet and its relationship with metabolic and inflammatory features in a cohort of patients with pSS.*

Methods. *Demographic, clinical and serological data, including anthropometric parameters and cardiovascular (CV) disease risk factors/events among others were collected from 91 pSS patients. Adherence to the Mediterranean diet over the previous 12 months was assessed with the 14-item PREvencion con DIeta MEDiterranea (PREDIMED) tool and the 28-item Mediterranean Lifestyle (MEDLIFE) index.*

Results. *According to the PREDIMED score 29 (31%) patients had a good adherence to the Mediterranean Diet, 57 (61%) a medium adherence and only 7 (8%) a poor adherence. No difference could be identified across groups with regard to demographic data, disease activity, CV risk factors or other parameters. With regard to the MEDLIFE, the total of blocks 1 and 2, that are related to Mediterranean foods and dietary habits, did not correlate with the total of block 3 (related to other healthy habits such as physical activity), meaning that the patients adhering the most to the Mediterranean Diet not necessarily had an overall healthy lifestyle. The PREDIMED score was inversely correlated with disease activity, as measured by ESSDAI (Spearman's rho=-0.27, p= 0.009) and ClinESSDAI (Spearman's rho=-0.26, p=0.01). Fish consumption was associated with lower prevalence of hypertension.*

Conclusion. *Adherence to the Mediterranean diet, with particular attention to fish consumption, may be beneficial on various domains in pSS, such as the CV system and the inflammatory environment, and as such should be recommended to patients with this disease.*

Introduction

The Mediterranean diet is a 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). The traditional diets of countries bordering the Mediterranean Sea represented different version of the Mediterranean diet. Historically, the observation that, despite their limited access to healthcare resources, people living in countries such as Greece and Southern Italy had lower incidence of chronic diseases and longer life expectancy drove the attention of the scientific community towards their dietary patterns. In early 1990s, the Harvard School of Public Health, Oldways Preservation and Exchange Trust, and the European Office of the World Health Organisation introduced the so-called 'Mediterranean diet pyramid'. This tool highlighted certain foods based on the dietary traditions of these areas during the mid-20th century (1, 2). To note, the Mediterranean diet pyramid also points to the importance of complementing healthy dietary pattern with regular physical activity.

Over the subsequent decades, a high number of studies demonstrated that adherence to the Mediterranean diet effectively reduced the risk of cardiovascular diseases, obesity, type 2 diabetes mellitus and all-cause mortality in the general population (3-11). Unfortunately, however, despite all this positive evidence, a Westernisation of the

diet has been increasingly observed, especially among the younger generations. This process, encompasses not only dietary changes such as a shift in the sources and proportion of dietary fats, but also other unhealthy lifestyle habits such as an increased sedentary life (12, 13). This adds a layer of complexity to the pursuit of effective CV prevention and requires the implementation of broader and more personalised approaches exploring in-depth the patient lifestyle (14).

The relationship between dietary habits, including the Mediterranean diet, and rheumatic and musculoskeletal diseases (RMDs) pertains not only to the knowledge that patients with RMDs display a higher cardiovascular risk compared to the general population, but also to the possible impact of nutrients at an earlier stage when the disease is not yet clinically evident (15-17).

In fact, diet may be one of the environmental factors associated with the development of RMDs as investigated in studies on large cohorts of healthy subjects (18-20). As far as primary Sjögren's syndrome (pSS) is concerned, Machowicz *et al*. demonstrated that adherence to the Mediterranean diet is associated with lower likelihood to be diagnosed with pSS in patients referring to a Rheumatology centre warranting investigation for this disease (21). However, data on patients with established pSS are lacking. The purpose of this study was to explore the adherence to the Mediterranean diet in a cohort of pSS patients and its relationship with metabolic and inflammatory features.

Materials and methods

Population study and inclusion criteria

We enrolled consecutive patients with pSS according to the 2016 American College of Rheumatology/European League against Rheumatism (ACR/EULAR) classification criteria (22). We excluded patients with SS associated with one or more systemic/organ-specific autoimmune diseases. This study was conducted in compliance with the protocol of Good Clinical Practices and Declaration of Helsinki principles.

Data collection and clinical assessment

Clinical and serological records were retrospectively evaluated and integrated with the data collected at enrolment. Disease activity was calculated with the EULAR Sjögren's syndrome disease activity index (ESSDAI) (23) while the patient perception of symptoms (overall dryness, ocular dryness, oral dryness, pain and fatigue) was reported on 0–10 visual analogue scales (VAS). The overall dryness, pain and fatigue VAS was also used to calculate the EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI) (24). Anthropometric parameters recorded were height and weight and used to calculate the body mass index (BMI) [weight (kg) divided by height squared (m2), kg/m^2].

The following CV disease risk factors were considered: smoking (defined as previous/current/no use of at least one cigarette/day), arterial hypertension (physician diagnosis and/or prior/ongoing antihypertensive therapy), hypercholesterolaemia (total serum cholesterol level >240 mg dL-1 in at least three assays), hypertriglyceridaemia (serum triglyceride level >150 mg dL-1 in at least three assays), high-density lipoprotein cholesterol (HDL-c) level (reduced <40 mg dL-1, normal 40–60 mg dL-1, increased >60 mg dL-1 in at least three assays), low-density lipoprotein cholesterol level (reduced <130 mg dL-1, normal 130–160 mg dL-1, increased >160 mg dL-1 in at least three assays), type 2 diabetes mellitus (DM) (ongoing treatment with insulin or oral hypoglycaemic agents and/or glucose level >126 mg dL-1 in at least two fasting glycaemia tests) and obesity (according to body mass index). The degree of obesity was established as follows: 25 ≤30 kg/m^2 (overweight), 30–34.9 kg/m^2 (grade I obesity), 35–39.9 kg/m^2 (grade II obesity), and ≥40 kg/m^2 (grade III obesity or severe obesity), respectively. We also considered hyperuricemia (cut-off serum uric acid (SUA) level to diagnose hyperuricemia 7.0 mg dL-1).

Metabolic syndrome was defined according to the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) criteria (25).

Cardiovascular (CV) events, namely myocardial infarction, angina, heart failure, cerebrovascular events, were recorded. We also considered arteriosclerotic vascular disease. CV events were recorded only if the diagnosis was confirmed by hospital discharge records and/or available specific laboratory and diagnostic examinations.

Osteoporosis was recorded only if the diagnosis was confirmed by hospital records and/or available specific diagnostic examinations. Vitamin D levels, alongside ongoing supplementation were also recorded.

Adherence to the Mediterranean Diet over the previous 12 months was assessed with the 14-item PREvencion con DIeta MEDiterranea (PREDIMED) tool (26). A total score ≤5 indicates poor adherence, between 6 and 9 medium adherence, ≥10 good adherence. The 28-item Mediterranean Lifestyle (MEDLIFE) index was also used (27). The MEDLIFE is structured as follows: Block 1 includes 15 questions on Mediterranean food consumption (*e.g*. How many serving of fish or seafood portions do you consume per week?); block 2 includes 7 questions on Mediterranean dietary habits (*e.g*. Do you usually choose whole grain products?); block 3 includes 6 questions on physical activity, rest, social habits and conviviality (*e.g*. Do you engage in physical activity (>150min/week or 30 min/day)?

Statistical analysis

Statistical analysis was performed with IBM SPSS 27.0. The Mann Whitney U- test or the Kruskal Wallis test were used to compare continuous variables while the χ^2 test was used for categorical variables. Bivariate correlation (Spearman's ϱ) and binary logistic regression analysis were also performed. All tests were two tailed and values of $p<0.05$ were considered statistically significant.

Results

Ninety-three pSS patients (95% females) referring to a Rheumatology Unit in the Abruzzo Region (the northernmost region of Southern Italy) were included in the study. Table I shows

their demographic and disease-specific features while Table II summarises the metabolic status, CV risk factors and related events. 44% of patients were either overweight or obese (Grade I or II) and 14 (15%) fulfilled the criteria for metabolic syndrome. Less than 30% of patients were current or past smokers while 41 (44%) had hypertension and 25 (27%) had hypercholesterolaemia. Overall, 24 patients (26%) had history of CV event and/or arteriosclerotic vascular disease. Of these, 18 (75%) reported only one CV event while 6 (25%) had experienced ≥2 CV event. Seventy-three (78%) patients reported taking vitamin D supplementation but only 28 of them had overt osteoporosis.

With regard to CV risk factors, BMI was directly correlated with ESSPRI, pain and fatigue (Sperman's rho 0.273, 0.268 and 0.228, respectively, all $p<0.05$) while patients with metabolic syndrome displayed higher levels of pain (0.02) and higher ESSPRI values ($p=0.05$).

As far as adherence to the Mediterranean diet was concerned, based on the PREDIMED tool 29 (31%) patients had a good adherence, 57 (61%) a medium adherence and only 7 (8%) a poor adherence. No difference could be identified across groups with regard to demographic data, disease activity, CV risk factors or other parameters (Table III). In more detail, it emerged that all patients used olive oil as main culinary lipid but consumption of sufficient servings per week of fish, nuts and legumes were reported by a low number of patients (24%, 29% and 43% respectively). In addition, only half of the patients reported the consumption of sufficient servings of fruit per day (Table IV). When assessing the impact of a reduced intake of such nutrients, we noticed a lower prevalence of hypertension in patients consuming sufficient servings per week of fish ($p<0.05$).

Unlike the PREDIMED score, the MEDLIFE index has no validated cut-off levels to define the extent of adherence to the Mediterranean diet. Furthermore, owing to its structure that is more complex than the PREDIMED, also encompassing the broader lifestyle habits, we analysed data by block of questions and by nutrient (Table V). The total of

Table I. Demographic and clinical characteristics of the patient cohort.

		Mean	SEM
Age (years)		61.8	1.2
Age at pSS diagnosis (years)		55.7	1.3
Disease duration (years)		6.2	0.5
VAS dryness		5.9	0.2
VAS xerostomia		6.1	0.3
VAS xerophthalmia		5.7	0.3
VAS pain		6.1	0.7
VAS fatigue		7.0	0.3
ESSPRI		6.3	0.3
ESSDAI		6.8	0.4
ClinESSDAI		6.5	0.4
		N	%
Female gender		88	95
Autoantibodies	Neither anti-Ro nor anti-La	53	57
	Anti-Ro only	23	25
	Both anti-Ro and anti-La	17	18
Therapy			
Systemic agents	HCQ	44	47
	other IS*	19	20
	low -dose GC	16	17

VAS: visual analogue scale; ESSPRI: EULAR Sjögren's Syndrome Patient Reported Index; ESSDAI: EULAR Sjögren's Syndrome Disease Activity Index; HCQ: hydroxychloroquine; IS: immunosuppressants; GC: glucocorticoids; SEM: standard error of the mean.
*leflunomide n=10, 53%; methotrexate n=7, 37%; sulfasalazine n=2; 10%.

Table II. Cardiovascular risk factors and events in the patient cohort.

		Mean	SEM
BMI (kg/m^2)		25.2	0.5
		N	%
Smoking	Current	10	11
	Former	17	18
	Never	66	71
Arterial hypertension		41	44
Hypercholesterolaemia		25	27
Hypertrygliceridaemia		15	16
LDL level	reduced	30	32
	normal	18	19
	increased	9	10
HDL level	reduced	5	5
	normal	33	35
	increased	20	22
T2D		3	3
Hyperuricaemia		4	4
Obesity	No	52	56
	Overweight	29	31
	Grade I obesity	8	9
	Grade II obesity	4	4
	Grade III obesity	0	0
Metabolic syndrome		14	15
CV event (number)	None	69	74
	1 event	18	19
	≥2 event	6	7
CV event type (n=24)			
	MI	1	4
	stroke	3	12
	TIA	13	54
	Angina	6	25
	HF	3	12
Atherosclerotic vascular disease		5	21

BMI: Body Mass Index; LDL: low density lipoproteins; HDL: high density lipoproteins; T2D: type 2 diabetes; CV: cardiovascular; MI: myocardial infarction; TIA: transient ischaemic attack; HF: heart failure; SEM: standard error of the mean.

Table III. Characteristics of patients according to the adherence to the Mediterranean diet calculated with the 14-item PREvencion con DIeta MEDiterranea (PREDIMED) tool.

		Poor	Medium	Good	*p*-value
Adherence to the Mediterranan diet (PREDIMED score)		≤5	6-9	≥10	
n (%)		7 (8)	57 (61)	29 (31)	
			Mean (SEM)		
Age (years)		59.9 (3.9)	59.8 (1.7)	66.2 (1.7)	0.09
Age at pSS diagnosis (years)		51.4 (4.8)	53.7 (1.8)	60.5 (1.8)	0.77
Disease duration (years)		8.4 (2.2)	6.1 (0.6)	5.7 (1.0)	0.34
ESSPRI		5.8 (0.6)	6.5 (0.4)	6.1 (0.4)	0.78
ESSDAI		8.9 (1.7)	7.1 (0.6)	5.7 (0.7)	0.12
ClinESSDAI		8.6 (1.7)	6.8 (0.6)	5.4 (0.6)	0.14
BMI (kg/m^2)		27.9 (2.1)	24.5 (0.5)	25.8 (0.9)	0.16
			N (%)		
Smoking					0.40
	Current	1 (14)	7 (12)	2 (7)	
	Former	3 (43)	9 (16)	5 (17)	
	Never	3 (43)	41 (72)	22 (76)	
Hypertension		2 (29)	26 (46)	13 (45)	0.69
Hypercholesterolaemia		2 (29)	13 (23)	10 (34)	0.51
Hypertrygliceridaemia		1 (14)	9 (16)	5 (17)	0.99
T2D		1 (14)	1 (2)	1 (3)	0.21
Hyperuricaemia		0	2 (3.5)	2 (7)	0.64
Obesity					0.21
	No	2 (29)	36 (63)	14 (48)	
	Overweight	3 (43)	17 (30)	9 (31)	
	Grade I obesity	1 (14)	2 (3.5)	5 (17)	
	Grade II obesity	1 (14)	2 (3.5)	1 (3)	
Metabolic syndrome		1 (14)	6 (10)	7 (24)	0.25
CV event (number)					0.75
	None	5 (71)	41 (72)	23 (79)	
	≥1 event	2 (29)	16 (28)	6 (21)	

SEM: standard error of the mean; ESSPRI: EULAR Sjögren's syndrome patient-reported index; ESSDAI: EULAR Sjögren's Syndrome Disease Activity index; BMI: Body Mass Index; T2D: Type 2 diabetes; CV: cardiovascular.

Table IV. Results by nutrient of the Mediterranean Diet calculated with the 14-item PREvencion con DIeta MEDiterranea (PREDIMED).

	PREDIMED item	n (%) patients
1	Use of olive oil as main culinary lipid	93 (100)
2	Olive oil >4 tablespoons	68 (73)
3	Vegetables ≥2 s/day	65 (70)
4	Fruits ≥3 s/day	47 (50)
5	Red/processed meats <1/day	82 (88)
6	Butter, cream, margarine <1/day	80 (86)
7	Soda drinks <1/day	52 (56)
8	Wine glasses ≥7/week	20 (21)
9	Legumes ≥3/week	40 (43)
10	Fish/seafood ≥3/week	22 (24)
11	Commercial sweets and confectionery ≤ 2/week	70 (75)
12	Tree nuts ≥3/week	27 (29)
13	Poultry more than red meats	62 (67)
14	Use of sofrito sauce ≥2/week	72 (75)

s: servings.

blocks 1 and 2, that are related to Mediterranean foods and dietary habits, did not correlate with the total of block 3, meaning that the patients adhering the most to the Mediterranean diet not necessarily had an overall healthy lifestyle. This was reinforced by the observation that the PREDIMED total score strongly correlated with the total of blocks 1 (Spearman's rho=0.52, $p<0.0001$) and block 2 (Spearman's rho=0.27, $p=0.008$) but not with the total of block 3 of the MEDLIFE score. Of note, 73 (78%) patients displayed low (≤3/6) partial scores of block 3, identifying widespread sedentary habits.

However, the blocks 1 and 2 were those affecting the most the final result and this was confirmed by the direct correlation between the MEDLIFE total score and the PREDIMED score (Spearman's rho=0.53, $p<0.0001$). With regard to individual nutrients/habits, the MEDLIFE explores additional areas compared to the PREDIMED such as the use of salt. 30% of patient reported preparing meals adding salt to taste rather than attempting to limit it as much as possible. Likewise, only 36 (39%) of patients usually choose wholegrain products over refined grains and only 27 (29%) of patients consumed adequate servings of cereals.

Table V. Results by blocks of questions of the 28-item Mediterranean Lifestyle (MEDLIFE) index.

	MEDLIFE item	n (%) of patients
	Block 1: Mediterranean food consumption	
1	Pastries ≤2 s/week	50 (54)
2	Red meat <2 s/week	68 (73)
3	Processed meat ≤ s/week	50 (54)
4	Eggs 2-4 s/week	68 (73)
5	Legumes ≥2/week	59 (63)
6	Poultry 2 s/week	59 (63)
7	Fish or seafood ≥2/week	45 (49)
8	Potatoes ≤3 s/week	81 (87)
9	Low-fat dairy 2 s/day	42 (45)
10	Nuts and olives 1-2 s/day	25 (27)
11	Herbs, spices or garnish ≥1 s/day	84 (90)
12	Fruit 3-6 s/day	43 (46)
13	Vegetables (except potatoes) ≥2 s/day	53 (57)
14	Olive oil ≥3 s/day	74 (80)
15	Cereals 3-6 s/day	27 (29)
	Block 2: Mediterranean dietary habits	
16	Water >6 glasses/day or at least one cup of tea/day	69 (74)
17	Wine at mealtime 1-2 s/day	17 (18)
18	Limited salt in meals	64 (69)
19	Choice of wholegrain products	36 (39)
20	Snacks (*e.g.* chips) ≤2 s/week	76 (82)
21	Limited nibbling between meals	64 (69)
22	Limit intake of sugar in beverages	65 (70)
	Block 3: Physical activity, rest, social habits and conviviality	
23	Physical activity >150 min/week or 30 min/day	45 (48)
24	Siesta/nap	37 (40)
25	Hours of sleep during weekdays 6-8 hour/day	57 (61)
26	Watching TV ≤1 hour/day	30 (32)
27	Going out with friends during free time ≥2 hour/weekend	50 (54)
28	Team sports ≥2 hour/week	11 (12)

s: servings.

Then, we sought to investigate any relationship between pSS-specific clinical parameters and PREDIMED and MEDLIFE scores. The PREDIMED score was inversely correlated with disease activity, as measured by ESSDAI (Spearman's rho=-0.27, p=0.009) and ClinESSDAI (Spearman's rho=-0.26, p=0.01). while neither the partial nor the total MEDLIFE scores correlated with any clinical parameter. As far as reported symptoms are concerned, neither the ESSPRI, nor any of VAS dryness scores, was correlated with the PREDIMED and MEDLIFE scores.

In line with the results pertaining to disease activity, a lower number of patients with medium and good adherence to the Mediterranean diet (higher PREDIMED scores) was treated with immunosuppressant agents (p=0.05). However, no difference was observed with regard to hydroxychloroquine, glucocorticoids and the PREDIMED or MEDLIFE scores.

Twenty-nine (31%) patients reported that due to the impaired salivary secretion they were unable to eat a variety of food. Of these, 11 (38%) patients are unable to eat bread and pasta, 5 (17%) patients are unable to eat acid food such as fruit and vegetables (*e.g.* tomatoes), 5 (17%) patients are unable to eat spicy food and 3 (10% patients) are unable to eat meat unless finely minced and nuts. These limitations did not consistently affect the adherence to the Mediterranean diet since these patients showed PREDIMED scores of 6 and over.

Discussion

To the best of our knowledge, this is the first study assessing adherence to the Mediterranean diet in patients with established pSS. We observed that over 90% of patients had a medium to good adherence as measured by the PREDIMED tool, however when complementing the results with the MEDLIFE index it emerged that only a few of them had an overall healthy lifestyle also including physical activity and adequate sleeping time among others.

In recent years, increasing evidence on the role of diet on a variety of chronic conditions, including CV disease, prompted researchers to focus on this topic also in the field of RMDs. In fact, food/nutrients have been associated with both the risk of developing these conditions in normal subjects and the natural history of the disease in patients with established RMDs, mainly rheumatoid arthritis (RA) (15-17, 28, 29).

However, since individual foods are part of complex dietary patterns, over the last years scores of overall dietary quality have received increasing attention (18-20).

The Mediterranean diet is a dietary pattern enriched in fiber, olive oil, a source of mono-unsaturated fatty acid and in fish, an important source of dietary n-3 poly-unsaturated fatty acid (PUFA). As far as diet and RMDs is concerned, the effects of this pattern have been assessed in two clinical trials in RA (30, 31) and in one cross-sectional study in systemic lupus erythematosus (SLE) (32). Although yielding encouraging results and proving that adherence to Mediterranean diet may be beneficial to improve disease activity (and in the case of SLE also disease damage), data are still too scarce to draw solid conclusions. Our results in pSS are in line with the above-mentioned studies in RA and SLE since we observed that disease activity was inversely correlated with the overall adherence to the Mediterranean diet. Taken together our data and those previously published in other RMDs underpin the concept that healthy dietary patterns rather than the use of individual nutrients should be advised.

As mentioned above, some components of the Mediterranean diet such as olive oil and fish are a source of mono-unsaturated (MU) and n-3 poly-unsaturated (PU) fatty acid (FA).

Interim data from the total management of risk factors in RA patients to lower morbidity and mortality (TOMOR-

ROW) study revealed that daily consumption of monounsaturated to saturated fatty acids (MUFA/SFA) as part of a Mediterranean diet is inversely correlated with disease activity while high MUFA intake is an independent predictor of remission in the RA (33). In addition to the intake as part of the Mediterranean diet, the effect of MUFA/PUFA supplementation has also been explored and deserves to be appraised. A recent meta-analysis of randomised controlled trials assessing the effect of n-3 PUFA supplementation in RA showed a slight but significant decrease of pain, tender joints, health assessment questionnaire and erythrocyte sedimentation rate (34). Likewise, a randomised controlled trial showed that the consumption of 10 ml per day of fish oil doubles the chance of achieving ACR remission in patients with early RA treated with a combination of conventional synthetic disease-modifying anti-rheumatic drugs (cs-DMARDs) (35).

In our cohort, all patients reported to use olive oil as the as main culinary lipid but only 24% of them consumed sufficient servings of fish per week. We did not observe differences in disease activity or other clinical features according to the fish intake but we cannot rule out that this may be masked at least in part by the adequate intake of olive oil in the majority of patients. In addition, only 2 patients reported taking omega-3 supplementation so a specific analysis on this subgroup could not be conducted. However, based on the data on RA, the use of PUFA supplementation may be an interesting area to explore also in pSS, particularly in patients with low intake of dietary fish.

It is interesting to note, that a lower prevalence of hypertension was observed in patients with adequate fish intake.

Fish consumption plays an important role in the modulation of blood pressure in hypertensive adults (36-38). Four meta-analyses of clinical trials demonstrated that fish oil or *n*-3 PUFA supplements can lower blood pressure in a dose dependent manner in hypertensive patients (39-42). and studies on animal models demonstrated that a diet enriched in *n*-3 PUFA is protective against blood pressure increase while dietary deficiency of n-3 PUFA in young rats was associated with development of hypertension in later life (43-45).

It is now well established that people with RMDs, including people with pSS have an increased CV risk due not only to conventional CV risk factors but also to the burden of chronic inflammation from the underlying RMD (46-48). Furthermore, we previously demonstrated that arterial hypertension is more prevalent in women with pSS compared to normal controls (49).

In light of this evidence, our results are of particular relevance since they point out that adherence to the Mediterranean diet, with particular attention to fish consumption, may be beneficial on various domains in pSS and as such should be recommended to patients with this disease.

Our study displays some limitations such as its cross-sectional nature, the low number of enrolled patients and the fact that it was conducted in a single centre within the Mediterranean area. However, we believe that it sets the stage for future research on this topic in order to clarify the immunological and metabolic effects of the Mediterranean diet in pSS.

References

1. WILLETT WC, SACKS F, TRICHOPOULOU A *et al*.: Mediterranean diet pyramid: a cultural model for healthy eating. *AJCN* 1995; 61: 1402S-6S.
2. GIFFORD KD: Dietary fats, eating guides, and public policy: history, critique, and recommendations. *Am J Med* 2002; 113: 89-106.
3. FUNG TT, REXRODE KM, MANTZOROS CS, MANSON JE, WILLETT WC, HU FB: Mediterranean diet and incidence of and mortality from coronary heart disease and stroke in women. *Circulation* 2009; 119: 1093-100.
4. LOPEZ-GARCIA E, RODRIGUEZ-ARTALEJO F, LI TY *et al*.: The Mediterranean-style dietary pattern and mortality among men and women with cardiovascular disease. *AJCN* 2013; 99: 172-80.
5. AHMAD S, MOORTHY MV, DEMLER OV *et al*.: Assessment of risk factors and biomarkers associated with risk of cardiovascular disease among women consuming a Mediterranean Diet. *JAMA* 2018; 1: e185708.
6. REES K, HARTLEY L, FLOWERS N, CLARKE A, THOROGOOD M, STRANGES S: Mediterranean' dietary pattern for the primary prevention of cardiovascular disease. *Cochrane Database Syst Rev* 2013; 8: CD009825.
7. ROSATO V, TEMPLE NJ, LA VECCHIA C, CASTELLAN G, TAVANI A, GUERCIO V: Mediterranean diet and cardiovascular disease: A systematic review and meta-analysis of observational studies. *Eur J Nutr* 2019; 58: 173-91.
8. ESTRUCH R, ROS E: Primary prevention of cardiovascular disease with a Mediterranean diet supplemented with extra-virgin olive oil or nuts. *N Engl J Med* 2018; 378: e34.
9. DONTAS AS, ZEREFOS NS, PANAGIOTAKOS DB, VALIS DA: Mediterranean diet and prevention of coronary heart disease in the velderly. *Clin Interv Aging* 2007; 2: 109-15.
10. HUO R, DU T, XU Y *et al*.: Effects of Mediterranean-style diet on glycemic control, weight loss and cardiovascular risk factors among type 2 diabetes individuals: A meta-analysis. *Eur J Clin Nutr* 2015; 69: 1200-8.
11. KASTORINI CM, MILIONIS HJ, ESPOSITO K, GIUGLIANO D, GOUDEVENOS JA, PANAGIOTAKOS DB: The effect of Mediterranean diet on metabolic syndrome and its components: A meta-analysis of 50 studies and 534,906 individuals. *J Am Coll Cardiol* 2011; 57: 1299-313.
12. GROSSO G, GALVANO F: Mediterranean diet adherence in children and adolescents in southern European countries. *NFS J* 2016; 3: 13-9.
13. KEARNEY J: Food Consumptions trends and drivers. *Phil Trans R Soc B Biol Sci* 2010; 365: 2793-807.
14. VOLPE M, BATTISTONI A, GALLO G, RUBATTU S, TOCCI G: Writing Committee; Scientific Societies. Executive Summary of the 2018 Joint Consensus Document on Cardiovascular Disease Prevention in Italy. *High Blood Press Cardiovasc Prev* 2018; 25: 327-41.
15. ALUNNO A, NIKIPHOROU E, PHILIPPOU E *et al*.: Nutrition in RMDs: is it really food for thought? Focus on rheumatoid arthritis. *BMC Rheumatol* 2020; 4: 10.
16. CUTOLO M, NIKIPHOROU E: Don't neglect nutrition in rheumatoid arthritis! *RMD Open* 2018; 4: e000591
17. ALUNNO A, CARUBBI F, BARTOLONI E, GRASSI D, FERRI C, GERLI R: Diet in rheumatoid arthritis versus systemic lupus erythematosus: Any differences? *Nutrients* 2021; 13: 772.
18. HU Y, SPARKS JA, MALSPEIS S *et al*.: Long-term dietary quality and risk of developing rheumatoid arthritis in women. *Ann Rheum Dis* 2017; 76: 1357-64.
19. TEDESCHI SK, BARBHAIYA M, SPARKS JA *et al*.: Dietary patterns and risk of systemic lupus erythematosus in women. *Lupus* 2020; 29: 67-73.
20. BARBHAIYA M, TEDESCHI S, SPARKS JA *et al*.: Association of dietary quality with risk of incident systemic lupus erythematosus in the Nurses' Health Studies. *Arthritis Care Res* (Hoboken) 2021; 73: 1250-8.
21. MACHOWICZ A, HALL I, DE PABLO P *et al*.: Mediterranean diet and risk of Sjögren's syndrome. *Clin Exp Rheumatol* 2020; 38 (Suppl. 126): S216-21.
22. SHIBOSKI CH, SHIBOSKI SC, SEROR R *et al*.: 2016 American College of Rheumatology/European league against rheumatism classification criteria for primary Sjögren's syndrome: A consensus and data-driven methodology involving three international patient cohorts. *Ann Rheum Dis* 2017; 76: 9-16.
23. SEROR R, RAVAUD P, BOWMAN SJ *et al*.:

EULAR Sjögren's syndrome disease activity index: development of a consensus systemic disease activity index for primary Sjögren's syndrome. *Ann Rheum Dis* 2010; 69: 1103-9.
24. SEROR R, RAVAUD P, MARIETTE X *et al*.: EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI): development of a consensus patient index for primary Sjögren's syndrome. *Ann Rheum Dis* 2011; 70: 968-72.
25. NATIONAL CHOLESTEROL EDUCATION PROGRAM (NCEP): Expert Panel on Detection and Treatment of High Blood Cholesterol in Adults. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation* 2002; 106, 3143-421.
26. MARTÍNEZ-GONZÁLEZ MA, GARCÍA-ARELLANO A, TOLEDO E *et al*.: A 14-item Mediterranean diet assessment tool and obesity indexes among high-risk subjects: the PREDIMED trial. *PLoS One* 2012; 7: e43134.
27. SOTOS-PRIETO M, SANTOS-BENEIT G, BODEGA P, POCOCK S, MATTEI J, PENALVO JL: Validation of a questionnaire to measure overall Mediterranean lifestyle habits for research application: the Mediterranean lifestyle index (MEDLIFE). *Nutr Hosp* 2015; 32: 1153-63.
28. PHILIPPOU E, NIKIPHOROU E: Are we really what we eat? Nutrition and its role in the onset of rheumatoid arthritis. *Autoimmun Rev* 2018; 17: 1074-7.
29. PETERSSON S, PHILIPPOU E, RODOMAR C, NIKIPHOROU E: The Mediterranean diet, fish oil supplements and Rheumatoid arthritis outcomes: evidence from clinical trials. *Autoimmun Rev* 2018; 17: 11105-14.
30. MCKELLAR G, MORRISON E, MCENTEGART A *et al*.: A pilot study of a Mediterranean-type diet intervention in female patients with rheumatoid arthritis living in areas of social deprivation in Glasgow. *Ann Rheum Dis* 2007; 66: 1239-43.
31. SKOLDSTAM L, HAGFORS L, JOHANSSON G: An experimental study of a Mediterranean diet intervention for patients with rheumatoid arthritis. *Ann Rheum Dis* 2003; 62: 208-14.
32. POCOVI-GERARDINO G, CORREA-RODRÍGUEZ M, CALLEJAS-RUBIO JL *et al*.: Beneficial effect of Mediterranean diet on disease activity and cardiovascular risk in systemic lupus erythematosus patients: a cross-sectional study. Rheumatology (Oxford) 2021; 60: 160-9.
33. MATSUMOTO Y, SUGIOKA Y, TADA M *et al*.: Monounsaturated fatty acids might be key factors in the Mediterranean diet that suppress rheumatoid arthritis disease activity: The TOMORROW study. *Clin Nutr* 2018; 37: 675-80.
34. GIOXARI A, KALIORA AC, MARANTIDOU F, PANAGIOTAKOS DP: Intake of ω-3 polyunsaturated fatty acids in patients with rheumatoid arthritis: A systematic review and meta-analysis. *Nutrition* 2018; 45: 114-124.e4.
35. JUNG SM, MIN HK, KOH JH: Salt aggravates arthritis by Th17 polarization. *Arthritis Rheumatol* 2014; 66 (Suppl. 11): S145.
36. DEL BRUTTO OH, MERA RM, GILLMAN J, CASTILLO PR, ZAMBRANO M, HA JE: Dietary oily fish intake and blood pressure levels: a population-based study. *J Clin Hypertens* (Greenwich) 2016; 18: 337-41.
37. COLUSSI G, CATENA C, DIALTI V, PEZZUTTO F, MOS L, SECHI LA: Fish meal supplementation and ambulatory blood pressure in patients with hypertension: relevance of baseline membrane fatty acid composition. *Am J Hypertens* 2014; 27: 471-81.
38. CABO J, ALONSO R, MATA P: Omega-3 fatty acids and blood pressure. *Br J Nutr* 2012; 107: S195-S200.
39. MORRIS MC, SACKS F, ROSNER B: Does fish oil lower blood pressure? Ameta-analysis of controlled trials. *Circulation* 1993; 88: 523-33.
40. MILLER PE, VAN ELSWYK M, ALEXANDER DD: Long-chain omega-3 fatty acids eicosapentaenoic acid and docosahexaenoic acid and blood pressure: a meta-analysis of randomized controlled trials. *Am J Hypertens* 2014; 27: 885-96.
41. GELEIJNSE JM, GILTAY EJ, GROBBEE DE, DONDERS AR, KOK FJ: Blood pressure response to fish oil supplementation: metaregression analysis of randomized trials. *J Hypertens* 2002; 20: 1493-9.
42. CAMPBELL F, DICKINSON HO, CRITCHLEY JA, FORD GA, BRADBURN M: A systematic review of fish-oil supplements for the prevention and treatment of hypertension. *Eur J Prev Cardiol* 2013; 20: 107-20.
43. VAN DEN ELSEN LW, SPIJKERS LJ, VAN DEN AKKER RF *et al*.: Dietary fish oil improves endothelial function and lowers blood pressure via suppression of sphingolipid-mediated contractions in spontaneously hypertensive rats. *J Hypertens* 2014; 32: 1050-8.
44. OGAWA A, SUZUKI Y, AOYAMA T, TAKEUCHI H: Dietary alpha-linolenic acid inhibits angiotensin-converting enzyme activity and mrna expression levels in the aorta of spontaneously hypertensive rats. *J Oleo Sci* 2009; 58: 355-60.
45. BEGG DP, PUSKAS LG, KITAJKA K *et al*.: Hypothalamic gene expression in omega-3 pufa-deficient male rats before, and following, development of hypertension. *Hypertens res* 2012; 35: 381-7.
46. HANSILDAAR R, VEDDER D, BANIAAMAM M, TAUSCHE AK, GERRITSEN M, NURMOHAMED MT: Cardiovascular risk in inflammatory arthritis: rheumatoid arthritis and gout. *Lancet Rheumatol* 2021; 3: e58-e70.
47. BARTOLONI E, ALUNNO A, CAFARO G *et al*.: Subclinical atherosclerosis in primary Sjögren's syndrome: does inflammation matter? *Front Immunol* 2019; 10: 817.
48. BARTOLONI E, BALDINI C, FERRO F *et al*.: Application of artificial neural network analysis in the evaluation of cardiovascular risk in primary Sjögren's syndrome: a novel pathogenetic scenario? *Clin Exp Rheumatol* 2019; 37 (Suppl. 118): S133-9
49. BARTOLONI E, BALDINI C, SCHILLACI G *et al*.: Cardiovascular disease risk burden in primary Sjögren's syndrome: results of a population-based multicentre cohort study. *J Intern Med* 2015; 278: 185-92.