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A randomized controlled trial investigating the effects of a mediterranean-like diet in patients with multiple sclerosis-associated cognitive impairments and fatigue

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Keywords
Cognition; Fatigue; Mediterranean Diet; Multiple Sclerosis; Healthy Diet

Abstract

Background: Among multiple sclerosis (MS) related symptoms and complications, fatigue might impact roughly 90% of patients. Decline in cognitive function is one of the other complications that occur in the first years after disease onset. The Mediterranean diet is one of the well-known anti-inflammatory dietary approaches. Therefore, this study aimed to explore the effects of a modified Mediterranean-like diet on cognitive changes and fatigue levels in comparison with a conventional standard diet over a 1-year follow-up.

Methods: In the current single-blind randomized controlled trial, 34 MS patients in the Mediterranean-like diet group and 38 patients in the standard healthy diet group were studied for 1 year. The dietary interventions were modified each month by an expert nutritionist. MS-associated fatigue level

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was evaluated using the Modified Fatigue Impact Scale (MFIS). Cognitive assessment was also performed using Minimal Assessment of Cognitive Function in MS (MACFIMS).

Results: Intergroup comparisons demonstrated that after considering confounding variables in ANCOVA, fatigue scores appeared significantly lower in patients who were treated with the Mediterranean-like diet than those in the standard healthy diet group [Mean 95% confidence interval (CI)}: 33.93 (32.97-34.89) and 37.98 (36.99-38.97), respectively; $P < 0.001$]. However, the intergroup analysis of cognitive status only showed a difference in the mean score of Brief Visuospatial Memory Test-Revised (BVMT-R) subtest of the MACFIMS. The BVMT-R was higher among standard healthy diet patients compared to the Mediterranean-like diet group after the intervention following adjustment for covariates [Mean (95% CI): 23.73 (21.88-25.57) and 20.56 (18.60-22.51), respectively; $P = 0.020$].

Conclusion: In conclusion, the results of this study highlighted the higher protective effects of the Mediterranean-like diet against MS-related fatigue than the standard healthy diet. However, no significant improvement was observed in the cognitive status of MS patients after a 1-year treatment with the Mediterranean-like diet. More randomized clinical trials with larger sample sizes are needed to elucidate the effects of dietary modifications on MS-associated symptoms and complications.

Introduction

Multiple sclerosis (MS) has been recognized as a chronic disabling disorder, with an autoimmune origin, which affects about 2500000 individuals in the world.[1] According to the registry system of the Iranian MS Society 1991-2014, it was estimated that approximately 101.39 per 100 thousand individuals in Tehran, the capital of Iran, are affected by MS during 1991-2014. Moreover, its prevalence has been rising with an alarming rate over the past 20 years. It was also mentioned that Tehran is ranked as one of the places with the highest prevalence of patients affected by MS.[2]

MS manifests through a variety of symptoms including sensory and motor impairment in extremities, ataxia, visual disturbances, fatigue, behavioral and emotional complications such as depressive symptoms, as well as cognitive decline. These different clinical manifestations appear according to the places of plaques/lesions within the brain and spinal cord, which occur subsequent to the demyelination of central nervous system (CNS) nerves and neurodegeneration. Symptoms become aggravated with the progression of destruction in the myelin sheath and neuronal transmission impairment. As is previously hypothesized, in addition to autoimmune processes, dysfunction in inflammatory responses also seems to be involved in the pathogenesis of MS.[1,3]

The disorder affects mostly young women aged between 20 and 40 years and particularly white adults.[1] Genetic vulnerability, immune system overactivation, and environment-related factors, including smoking, childhood obesity, low 25-hydroxyvitamin D (25-OH-D) concentration, and diet-associated factors, are among the proposed risk factors for MS.[4]

Although several treatment strategies are available for MS, a specific strategy has not been established to date. Current procedures can only relieve symptoms, reduce the number of relapses, and control or modify disease progression, mainly through the inhibition of immune system activation. Thus, there is still a need for new treatment options to alleviate MS, control accompanied symptoms, and reduce the impact of MS on patients' life.[1]

Among MS-related symptoms and complications, fatigue might impact roughly 90% of patients and can also occur at a very early stage of disease development. Thus, due to its adverse effects on different aspects of a person's life, including a decline in physical, mental, psychological, and social abilities, particularly cognition,[3] designing interventions to alleviate MS-related fatigue could lead to an improvement in patients' overall quality of life (QOL).

Moreover, a decline in cognitive function is one of the other MS-related complications that could occur in the initial years of disease onset.[5,6] Some of the suggested risk factors of cognitive impairment in MS patients include genetics, age, and the male gender.[7] However, it seems that there is no established and highly effective therapy to combat the cognitive decline of different disorders. In this regard, nonpharmacological options such as neuropsychological interventions and dietary modifications have been studied previously; however, their effectiveness is still under investigation.[6]

The role of diet in the development, progression, and alleviation of MS-associated symptoms has been examined in a number of studies. For example, it has been suggested that following a gluten-free diet, having a diet with a high amount of plant-based foods (vegetables and fruits) and low amount of high-fat animal-based

foods (meat and dairy), or increasing the intake of some beneficial dietary components such as unsaturated fatty acids, nutritional antioxidants, and anti-inflammatory agents may also be useful in preventing and/or controlling MS progression. There is, however, still no consensus for dietary advice in these patients, mostly because of the limitations of the previously designed trials, including a small number of studied subjects, short duration of research, and failure to use double-blind techniques.[4,6,8-11]

The Mediterranean diet is characterized by high amounts of mono-unsaturated and poly-unsaturated fatty acids (MUFA and PUFA) and, conversely, low amounts of saturated fats along with high-fiber consumption. The diet is also comprised of a high content of anti-inflammatory foods and nutrients such as olive oil, fresh fruit, vegetables, and other plant foods, whole grains, as well as fish and seafood; in contrast, a limited intake of high-fat meats, sweets, and processed foods is recommended.[12] The Mediterranean diet is one of the popular complementary approaches to treating a variety of conditions, especially obesity, metabolic syndrome, diabetes, cardiovascular diseases (CVD), neurodegenerative diseases, and chronic inflammatory disorders. A growing body of evidence showed the protective effects of the Mediterranean diet against inflammation in rheumatoid arthritis and Crohn's disease, obesity, CVD, and even in healthy subjects via suppressing the expression of a number of pro-inflammatory factors [tumor necrosis factor (TNF-α), Interleukin-1 (IL-1), and IL-6], improving endothelial function, and enhancing the antioxidant capacity of the body. It has also been proposed that this type of diet might be related to decreased MS risk.[12-15]

Therefore, the current single-blind, randomized, controlled trial aims to contribute to this growing area of research by exploring the effects of a modified Mediterranean-like diet on MS-associated cognitive changes and fatigue levels in comparison with a standard healthy diet over a 1-year follow-up period.

Materials and Methods

Study participants and randomization: All study participants of this single-blind, randomized, 1-year clinical trial have been recruited from the MS clinic of Sina University Hospital, Tehran University of Medical Sciences, Tehran, Iran. From among about 115 relapsing-remitting MS (RRMS) patients, who had the study inclusion criteria, 80 patients were enrolled in the study. We used recommendations of the "Multiple Sclerosis Clinical Trials: Part 1"[16] as the basis for determining the inclusion/exclusion criteria. Moreover, these criteria were established to reduce the source of bias in the interpretation of results.[17-19] The inclusion criteria (and its rationale) were the diagnosis of RRMS based on the McDonald 2010 MS diagnostic criteria (due to the progressive nature of other types of MS and higher prevalence of RRMS), undergoing beta-interferon treatment (to rule out effects of different treatment modalities and various types of drugs that could be a source of bias in the interpretation of results), an Expanded Disability Status Scale (EDSS) score of < 5.5 (to include more independent patients and less disabled subjects because of the nature of the intervention, a dietary intervention, which necessitates the patients to be independent to follow the instructions for preparing 5 meals a day, etc.), an age of 18-55 years and body mass index (BMI) of 18-30 kg/m^2 (to reduce the effect of obesity and BMI of more than 30 on MS progression and response to dietary intervention).[17] To eliminate the effects of corticosteroids on the immune system, all patients were in the remitting phase with no relapse over the past 3 months before the study. Changes in disease-modifying therapy during the study and consumption of cytotoxic medications, antipsychotic drugs, and cortisone were considered as the exclusion criteria because of their probable effects on weight gain and the response to dietary interventions,[20] and their likely impact on cognitive status and fatigue[21,22] as the outcomes of the study. Having a history of drug abuse, following any special diet because of medical reasons, suffering from any neurological condition other than MS, and psychologic or chronic disorders including head trauma, tumors, eating disorder, major depression, CVD, as well as endocrine, metabolic, liver, or kidney impairment were the other exclusion criteria. Subjects who were pregnant, breastfed, or had a planned pregnancy were also excluded. Prior to enrollment, information on the research procedures and objectives were given to all participants. Furthermore, written informed consent was obtained from all participants.

The study protocol was approved in the institutional review board of the Iranian

center of neurological research (research number = 93-02-54-24463) and received ethical approval from the ethics committee of Tehran University of Medical Sciences (93-02-54-24463-316140).

Demographic and anthropometric data and clinical assessments: After enrollment, all patients were initially examined by our medical team, including expert MS-specialist neurologists, a physician, a registered dietitian, a sports medicine specialist, and a clinical psychologist. Data on demographic and socioeconomic characteristics such as age, sex, educational level, and job were collected at baseline.

Bodyweight was assessed on a Seca 755 dial column medical scale with a weighing accuracy of 0.5 kg, and height was measured using a standard stadiometer with an accuracy of 0.1 cm. BMI was estimated by dividing weight in kg by height in square meter.

At the beginning of the study, a neurological examination was performed to assess the level of disability using the Kurtzke EDSS and 25-foot walk test (25-FWT).

Furthermore, data on past medical history and MS-related features, including the duration of disease onset, disease progression status, relapse rate during the last year, and drug abuse history, were also recorded at baseline.

Fatigue Assessment: MS-associated fatigue level was evaluated using the Modified Fatigue Impact Scale (MFIS), which was previously validated in the Iranian population. This 21-item questionnaire includes 9 items to assess physical status, 9 items to determine cognitive status, and 2 items to evaluate the psychosocial function status.[23]

Cognitive Assessment: cognitive assessment was performed at baseline and after a 1-year trial using a reliable and validated cognitive questionnaire [Minimal Assessment of Cognitive Function in MS (MACFIMS)]. The MACFIMS consists of different subtests including subtests for assessing memory and mental and visual processing speed [Paced Auditory Serial Addition Test (PASAT), Symbol Digit Modalities Test (SDMT), the California Verbal Learning Test-2nd edition (CVLT-II), CVLT-II delayed recall, and Brief Visuospatial Memory Test-Revised (BVMT-R)], evaluating language [Controlled Oral Word Association Test (COWAT)], spatial processing assessment [Judgment of Line Orientation Test (JLO)], and executive function evaluation (Delis-Kaplan Executive Function System (D-KEFS) description score and DKEFS total sorting score).[24]

Intervention: A registered dietitian interviewed all patients. Data on usual dietary intake of study participants were collected using 24-hour diet recall for 3 days (2 working days and 1 day on the weekend) to prescribe the specific diet for each subject considering her/his usual dietary habits and preferences. At the first visit, the energy requirement was calculated according to individuals' anthropometric assessments. After that, nutritional needs and macronutrient needs (protein, carbohydrate, and fat) were estimated. The distribution of macronutrients in the prescribed diet for patients in both groups was 18-20% for protein, 30% for lipid, and 50-52% for carbohydrate. Then, patients were visited by the same dietitian monthly until the end of the study, and their prescribed diet was adjusted according to the new weight assessments.

The energy needs and macronutrients were proportionate to the participants' age, sex, and BMI. In general, the intervention diet was modified in accordance with the Mediterranean diet, except for wine and some other unspecified foods. Thus, some special dietary instructions were made for patients in the Mediterranean-like diet group. The advice mainly focused on encouraging the increasing of the consumption of healthy oils (especially olive and olive oil), whole grains, vegetables, fruits and raw and unroasted nuts and seeds, legumes, and healthy plant based foods. Moreover, the consumption of fish and seafood (for about 2 times per week), poultry, eggs, and low fat or skimmed dairy (daily to weekly) was recommended. Furthermore, the participants were instructed to limit the intake of red meat, fried foods, and refined grains in addition to minimize the consumption of simple sugar, sugary foods and beverages, processed meat, and animal based fats to as low amounts as possible. The main modification that was made to the original Mediterranean diet included eliminating wine and some types of foods according to the Iranian culture based on religious beliefs. It is worth noting that all study participants were Muslim.

Moreover, the participants' usual diet was not a standard healthy diet, but rather a nutritionist-aided diet in accordance with the United States Department of Agriculture (USDA) dietary guidelines for Americans, 2010. The guidelines were customized in macronutrients to be proportionate to the patients' age, sex, and BMI.

Furthermore, these guidelines propose food-based recommendations for promoting public health, attempting to ensure patients' dietary requirements have been met, and preventing the development and progression of chronic disease.

Patients in both groups were recommended to have 5 meals each day. In addition, the participants were not aware of the treatment they received (i.e., they did not know whether the diet they received is the control diet or the Mediterranean-like diet). The Mediterranean-like diet adherence scores were assessed by applying a 6-item questionnaire (scored from 0 to 14) every 12 weeks during the study, the higher the value, the higher the adherence to the Mediterranean-like diet.

Sample Size Calculation and Statistical Methods: Randomization was performed using block randomization methods based on pre-generated randomization code lists provided by the "http://www.randomization.com" website. Thus, 40 patients were randomly allocated to each arm of the study in multiple blocks of 4 and 1:1 ratio according to age and sex. Only the researchers were aware of the assigned dietary intervention (standard healthy diet or the Mediterranean-like diet).

The normality of data was assessed using the Kolmogorov-Smirnov test. Categorical variables were analyzed, applying the chi-squared test. The +paired t-test or Wilcoxon signed-rank test was applied for the comparison of intragroup changes in variables. In addition, independent sample t-test or Mann–Whitney U test was used to make intergroup comparisons. Moreover, intergroup differences at the end of the trial were determined using the analysis of covariance (ANCOVA) test adjusted for age, changes in the Mediterranean-like diet adherence scores, and BMI, in addition to the baseline value of each variable. Data are presented as mean [standard deviation (SD)], median [interquartile range (IQR)], percentages, and ANCOVA-derived adjusted means and 95% confidence interval (CI) when appropriate. A two-sided p-value < 0.05 was considered as statistically significant. All data analysis was performed using SPSS software (version 19, Chicago, IL, USA).

Results

From among 115 patients, 80 individuals met the study inclusion criteria and were randomly allocated to either the Mediterranean-like diet or standard healthy diet group. In addition, 6 patients in the Mediterranean-like diet group (n = 34) and 2 patients (n = 38) in the standard healthy diet group were excluded from the study (Figure 1).

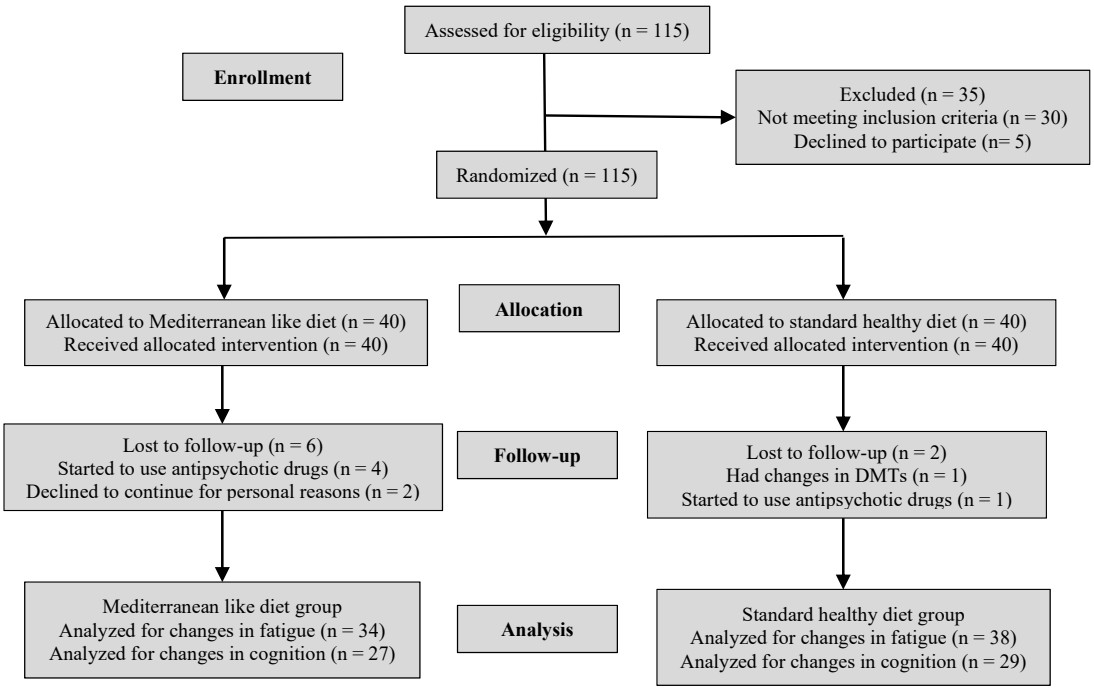

Figure 1. CONSORT 2010 Flow Diagram for Study Participants

Table 1. Baseline characteristics and clinical assessments of patients in the studied groups

Variable	Mediterranean-like diet group (n = 34)	Standard healthy diet group (n = 38)	P
Female Sex [n (%)]	31 (91.2)	33 (86.8)	0.55
Family history of autoimmune disorders[n (%)]	14 (50.0)	13 (38.2)	0.35
Age (year) (mean ± SD)	34 ± 8	34 ± 9	0.87
Education (year) (mean ± SD)	14 ± 3	14 ± 3	0.93
MS Disease Duration (year) (mean ± SD)	8 ± 5	8 ± 5	0.78
Total EDSS score (mean ± SD)	2.27 ± 1.14	2.40 ± 1.07	0.65
Total 25-FWT score (mean ± SD)	10.07 ± 4.5	10.50 ± 3.23	0.87

MS: Multiple Sclerosis; EDSS: Expanded Disability Status Scale; 25-FWT: 25-foot walk test; SD: Standard deviation

Finally, 72 subjects completed the survey. About 91.2% of patients in the Mediterranean-like diet group and 86.8% of standard healthy diet group consisted of women. The mean (SD) of age in the studied subjects in the Mediterranean-like diet and standard healthy diet groups was 34 (8) and 34 (9) years, respectively. No differences were observed between the groups in terms of baseline disease-related factors (Table 1).

Figure 2 presents the studied groups' adherence to the Mediterranean diet advises at 4 study time points. Each time point represents the data obtained every 12 weeks during a year of follow-up. Although no significant differences were observed between the two groups at baseline, the adherence to this diet was higher in the groups who underwent treatment with the Mediterranean-like diet. Mean (SD) Mediterranean diet adherence scores were 9.45 (2.49) in the Mediterranean-like diet group versus 7.00 (2.54) in the standard healthy diet group at the end of the trial (P < 0.001).

Changes in fatigue levels of the studied groups, according to MFIS scores, are presented in table 2. At baseline, the mean fatigue score was significantly higher among patients who were randomly allocated to the Mediterranean-like diet group than the subjects in the standard healthy diet (P = 0.040). After 1 year of treatment with either of the two diets, levels of fatigue significantly decreased within both groups (P < 0.050). However, this reduction was more significant in the Mediterranean-like diet group (P < 0.001). After considering age, changes in the Mediterranean diet adherence scores, changes in BMI, and fatigue scores at baseline in ANCOVA, fatigue scores also appeared significantly lower in the patients who were treated with the Mediterranean-like diet than those in the standard healthy diet group after a year of follow-up (P < 0.001) (Table 2).

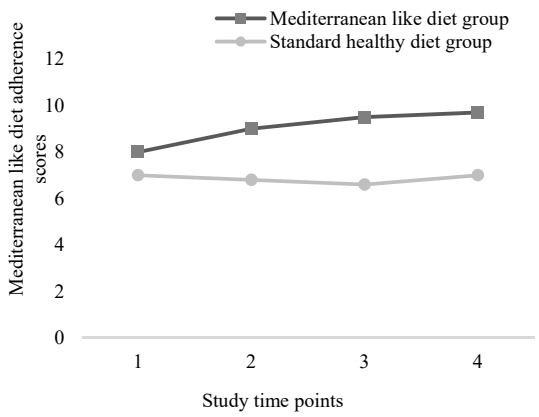

Table 2. Changes in body mass index (BMI) and fatigue levels in the studied groups during the study relative to baseline

Variable	Mediterranean-like diet group (n = 34)	Standard healthy diet group (n = 38)	P
BMI at baseline	27.34 (2.98)	27.67 (1.15)	0.550*
BMI after the intervention	26.01 ± 2.73	27.29 ± 1.29	0.020*
P#	< 0.001	< 0.001	
Fatigue score at baseline	40.05 ± 4.22	38.19 ± 4.01	0.040*
Fatigue score after the intervention	35.30 ± 4.20	37.48 ± 4.36	0.030*
Adjusted fatigue score after the intervention	33.93 (32.97-34.89)	37.98 (36.99-38.97)	< 0.001**
P#	< 0.001	0.030	

*Intergroup comparisons using independent t-test or Mann–Whitney U test, **Intergroup comparisons using ANCOVA test adjusted for age, MS disease duration, changes in the Mediterranean-like diet adherence score, changes in BMI levels, and baseline scores of fatigue, #Intragroup comparisons using paired t-test or Wilcoxon signed ranking test

Data were presented as mean ± SD or median (IQR) or adjusted mean (95% CI) as appropriate.

P < 0.05 was considered as significant.

BMI: body mass index

No significant differences were observed between the study groups in terms of PASAT, SDMT, CVLT-II total learning, CVLT-II delayed recall scores, JLO, NAART, COWAT, MC9HPT, and NONDOM subtests. However, the BVMT-R subtest score was shown to be significantly higher among standard diet patients after the intervention following adjustment for covariates in ANCOVA (P = 0.020). Regarding intragroup changes, CVLT-II total learning score significantly increased among the standard healthy diet group participants, D-KEFS description score slightly decreased among patients in both groups, and DKEFS total sorting score significantly reduced only in the Mediterranean-like diet group (P < 0.050); in contrast, no significant changes were observed in the scores of other subtests in each of the study arms (Table 3).

Table 3. Changes in cognitive status according to Minimal Assessment of Cognitive Function in Multiple sclerosis subtests scores in the studied groups during the study relative to baseline

Variable	Mediterranean-like diet group (n = 27)	Standard healthy diet group (n = 29)	P
PASAT at baseline	41.07 ±16.67	41.18 ± 16.86	0.970*
PASAT after the intervention	44.11 ± 13.01	41.28 ± 19.02	0.510*
Adjusted PASAT after the intervention	42.68 (39.89-45.47)	42.37 (39.73-45.01)	0.870**
P#	0.250	0.960	
SDMT at baseline	44.96 ± 13.07	43.00 ± 11.44	0.530*
SDMT after the intervention	44.77 ± 13.48	43.00 ± 11.44	0.670*
Adjusted SDMT after the intervention	43.37 (40.70-46.04)	45.89 (43.37-48.42)	0.190**
P#	0.410	0.660	
CVLT-II delayed recall at baseline	10.39 ± 2.98	11.00 ± 3.11	0.440*
CVLT-II delayed recall after the intervention	11.14 ± 2.95	11.15 ± 3.01	0.990*
Adjusted CVLT-II delayed recall after the intervention	11.50 (10.31-12.69)	10.12 (8.96-11.28)	0.110**
P#	0.120	0.900	
CVLT-II Total learning at baseline	49.39 ± 9.32	50.62 ± 8.90	0.520*
CVLT-II Total learning after the intervention	47.90 ± 8.82	51.56 ± 10.57	0.720*
Adjusted CVLT-II delayed recall after the intervention	50.79 (47.08-54.49)	50.94 (47.24-54.64)	0.950**
P#	0.500	0.040	
JLO at baseline	20.29 ± 5.14	18.13 ± 5.10	0.100*
JLO after the intervention	19.37 ± 5.30	18.72 ± 5.32	0.640*
Adjusted JLO after the intervention	18.62 (17.27-19.97)	19.57 (18.30-20.85)	0.330**
P#	0.210	0.130	
NAART at baseline	43.00 (5.00)	42.00 (6.25)	0.150*
NAART after the intervention	42.00 (4.00)	43.00 (6.00)	0.170*
Adjusted NAART after the intervention	41.52 (40.21-42.83)	40.95 (39.71-42.19)	0.550**
P#	0.970	0.980	
BVMT-R at baseline	21.96 ± 8.55	22.22 ± 7.39	0.900*
BVMT-R after the intervention	21.56 ± 9.34	23.81 ± 7.31	0.300*
Adjusted BVMT-R after the intervention	20.56 (18.60-22.51)	23.73 (21.88-25.57)	0.020
P#	0.510	0.060	
COWAT at baseline	9.37 ± 3.52)	7.99 ± 3.08	0.110*
COWAT after the intervention	9.42 ± 3.60)	8.10 ± 2.72	0.110*
Adjusted COWAT after the intervention	8.82 (8.02-9.61)	8.63 (7.89-9.38)	0.750**
P#	0.86	0.700	
D-KEFS description score at baseline	13.70 ± 4.92	12.56 ± 5.38	0.400*
D-KEFS description score after the intervention	11.98 ± 4.96	11.22 ± 5.06	0.560*
Adjusted D-KEFS description score after the intervention	10.97 (9.45-12.49)	11.69 (10.25-13.12)	0.510**
P#	< 0.001	< 0.001	
D-KEFS total sorting score at baseline	3.68 ± 1.31	3.39 ± 1.37	0.400*
D-KEFS total sorting score after the intervention	3.22 ± 1.32	3.22 ± 1.33	0.990*
Adjusted D-KEFS total sorting score after the intervention	2.92 (2.48-3.36)	3.39 (2.98-3.81)	0.140**
P#	< 0.001	0.220	

*Intergroup comparisons using independent t-test or Mann-Whitney U test, **Intergroup comparisons using ANCOVA test adjusted for age, MS disease duration, changes in the Mediterranean-like diet adherence score, changes in BMI levels, and baseline scores of subtests, #Intragroup comparisons using paired t-test or Wilcoxon signed ranking test

Data were presented as mean ± SD or median (IQR) or adjusted mean (95% CI) as appropriate.

P < 0.05 was considered as significant.

BMI: body mass index; MACFIMS: Minimal Assessment of Cognitive Function in MS patients; PASAT: Paced Auditory Serial Addition Test; SDMT: Symbol Digit Modalities Test, CVLT-II: California Verbal Learning Test second edition; BVMT-R: Brief Visuospatial Memory Test-Revised; COWAT: Controlled Oral Word Association Test; JLO: Judgment of Line Orientation Test; D-KEFS: Delis-Kaplan Executive Function System description

Discussion

Diet and fatigue: The results regarding the effects of diet on fatigue demonstrated the ameliorating effects of both Mediterranean-like and standard healthy diet on fatigue levels after a 1-year intervention. Albeit this improving effect was more pronounced among patients who were treated with the Mediterranean-like diet, even after controlling for age, changes in BMI levels, and the Mediterranean-like diet adherence scores in addition to fatigue scores at baseline in ANCOVA.

The more significant effects of the Mediterranean-like diet on fatigue could be explained through various mechanisms. Approximately 80% of patients with MS experience different levels of fatigue, and this complication has been established as one of the main disabling symptoms related to MS.[25] MS is recognized as a disorder with an imbalance in T cells production toward augmented activation of T helper 1 and 17 and disturbed function of regulatory T cells. In addition, evidence shows that the concentration of TNF-α, a pro-inflammatory factor, might act as a predictor for disease progression in MS sufferers. Moreover, it seems that there might be a correlation between the level of several inflammatory markers and MS-associated fatigue.[25] In this regard, a review study reported that the augmented concentrations of IFNγ, TNF-α, and IL-6 might be related to fatigue levels in MS subjects.[3] Furthermore, although the effects of diet on MS-associated symptoms and complications are not entirely understood,[26] the protective effect of the Mediterranean-like diet, which is mainly composed of a variety of antioxidants, fiber, and unsaturated fatty acids especially olive oil, on inflammation through suppressing inflammatory markers such as CRP, IL-6, and TNF-α has been confirmed in a growing body of research.[27-30]

Our findings are in agreement with those obtained by Yadav et al.[31] In this study, the researchers examined the effects of a plant-based diet with very low fat content (n = 32 MS patients) compared to a control diet (n = 29 MS patients). They observed that this diet could significantly attenuate MS-related fatigue level which was assessed using the Fatigue Severity Scale (FSS) (4.89 at baseline, -0.06 points per month reduction) and MFIS-short version (9.87 at baseline, -0.23 points per month reduction), during a year of intervention. In contrast, there were no differences between the study groups in terms of brain MRI results, MS relapse rate, and disability level; however, the study was not powered to find differences in these endpoints.[31]

Furthermore, it has been suggested that MS patients with higher BMI levels may experience higher fatigue levels.[32] In the current study, the BMI of the patients in both groups significantly reduced, which might also be involved in attenuating fatigue levels in the studied subjects.

Diet and cognition: In our study, MACFIMS subtests, which assess the verbal and learning memory, auditory information processing speed and flexibility and calculation ability, attention, speed of information processing visuospatial ability, verbal fluency, and executive function, did not reveal any significant differences between the studied groups neither at the beginning of the study nor after a year of follow-up. Only after controlling for confounding variables, the BVMT-R subtest score that evaluates visual learning and visual memory was significantly higher among patients in the standard healthy diet group. Furthermore, intragroup comparisons showed a slight decrease in the executive function scores assessed using the D-KEFS description score in both studied groups and sorting abilities evaluated by the D-KEFS sorting score among patients who underwent the Mediterranean-like diet intervention. Furthermore, CVLT-II total learning score that assessed verbal learning changes significantly increased in the standard healthy diet group.

These findings regarding the effects of diet on cognition differ from some previous studies. A cross-sectional study on 70 patients suffering from MS in comparison with 142 healthy subjects showed the higher the adherence to the Mediterranean diet, the lower the risk of MS.[13] Moreover, in a randomized controlled trial on 20 MS patients investigating the effects of a 6-month Mediterranean diet following calorie restriction for about 10 days, it was shown that the intervention resulted in increased levels of attention and memory.[33] However, these results should be interpreted with caution because it is not possible to distinguish the effects of the interventions separately. In addition, the lack of a control group made it difficult to interpret the findings.[33] Regarding our results, it is noteworthy that the relatively high adherence to the Mediterranean diet at baseline and throughout the study, which was observed in both groups, might be related to the main modifications that

were made to the original Mediterranean diet. These modifications included eliminating wine and some types of foods according to the Iranian culture based on religious beliefs. Moreover, as mentioned in the methods section, the average macronutrient content of the diets was similar.

In addition, existing evidence shows the protective role of the Mediterranean diet against cognition decline, especially in the elderly and individuals with dementia. Nevertheless, it is noteworthy that this proposed effect is mainly based on cross-sectional studies in which the association between the Mediterranean-like diet and age-related cognitive decline has been evaluated. According to the concluding remarks of the review studies concerning this association, more robust clinical trials and longitudinal studies are warranted in order to confirm the improving outcomes of the Mediterranean diet in cognitive impairment.[34-37]

Although our research was unsuccessful in proving the positive effects of a year of the Mediterranean-like diet intervention on cognitive functions in MS patients, there could be some explanations. MS-related impairment in cognitive function is an essential reason for the disability that could be attributed to brain tissue damage, indicators of its atrophy, and macroscopic MS lesions.[7] Genetic factors, age, and being male are of the most commonly recognized risk factors for cognitive dysfunction among these patients.[7] As mentioned, it is noteworthy that a decline in cognitive function could occur during the first years after disease onset even when the level of disability is not necessarily affected by disease progression.[5,6] Moreover, the mean duration of disease among studied groups in this trial was about 8 years, which might not be an appropriate time to prevent or attenuate impaired cognition in MS patients. Furthermore, previous studies have shown that non-pharmacological treatments could hardly affect cognitive function in MS subjects.[5] In addition, it has been emphasized that the level of depressive symptoms affect different aspects of cognitive function and could be an important factor in determining the cognitive status in patients.[7] However, the depression status of patients was not evaluated in this study.

In an open-label study by Lee et al., the effects of a multi-intervention strategy consisting of a modified version of a modified Paleolithic diet (that excluded gluten sources in the diet, dairy, and eggs, and increased the intake of vegetables, animal, and plant-based protein, and omega 3 rich oils), exercise practices, stress management, and neuromuscular electrical stimulation (NMES) on 19 MS subjects were investigated.[6] It was demonstrated that during a 1-year intervention, cognition and depression status improved significantly.[6] Moreover, these improvements occurred concurrently with an enhancement of fatigue level in patients.[6]

Our study had some strengths and weaknesses. First, as mentioned, we did not assess the changes in depression scores of the study participants. Second, the consumption of dietary supplements was not recorded. Third, the comorbidities of MS patients and their impact on patients' overall health status, QOL, and response to treatment were not investigated. Fourth, we were not able to explore the exact energy consumption or expenditure out of the prescribed daily calorie for each individual. Fifth, the near-significant higher adherence to the Mediterranean diet at baseline, which was observed in the control arm, might be a source of bias.

The study strengths include the low dropout rate, long-term duration of the study follow-up, and the definite diagnosis of RRMS according to examination by an expert MS-specialist neurologist based on the McDonald 2010 MS diagnostic criteria. Moreover, the same drug treatment was applied for all studied patients who could reduce the risk of bias in study results interpretation.

Conclusion

In conclusion, the results of this study highlighted the higher protective effects of the Mediterranean-like diet against MS-related fatigue than the standard healthy diet, even after controlling for age, changes in BMI levels, the Mediterranean-like diet adherence scores, and fatigue levels at baseline. However, no significant improvement was observed in the cognitive status of MS patients after a year of dietary intervention. More randomized clinical trials with larger sample sizes are needed to elucidate the effects of dietary modifications on MS-associated symptoms and complications.

Conflict of Interests

The authors declare no conflict of interest in this study.

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None.

References

1. Tillery EE, Clements JN, Howard Z. What's new in multiple sclerosis? Ment Health Clin 2017; 7(5): 213-20.
2. Eskandarieh S, Heydarpour P, Elhami SR, Sahraian MA. Prevalence and incidence of multiple sclerosis in Tehran, Iran. Iran J Public Health 2017; 46(5): 699-704.
3. Chalah MA, Ayache SS. Is there a link between inflammation and fatigue in multiple sclerosis? J Inflamm Res 2018; 11: 253-64.
4. Riccio P, Rossano R, Larocca M, Trotta V, Mennella I, Vitaglione P, et al. Anti-inflammatory nutritional intervention in patients with relapsing-remitting and primary-progressive multiple sclerosis: A pilot study. Exp Biol Med (Maywood) 2016; 241(6): 620-35.
5. Messinis L, Kosmidis MH, Lyros E, Papathanasopoulos P. Assessment and rehabilitation of cognitive impairment in multiple sclerosis. Int Rev Psychiatry 2010; 22(1): 22-34.
6. Lee JE, Bisht B, Hall MJ, Rubenstein LM, Louison R, Klein DT, et al. A multimodal, nonpharmacologic intervention improves mood and cognitive function in people with multiple sclerosis. J Am Coll Nutr 2017; 36(3): 150-68.
7. Rimkus CM, Steenwijk MD, Barkhof F. Causes, effects and connectivity changes in MS-related cognitive decline. Dement Neuropsychol 2016; 10(1): 2-11.
8. Altowaijri G, Fryman A, Yadav V. Dietary interventions and multiple sclerosis. Curr Neurol Neurosci Rep 2017; 17(3): 28.
9. Bagur MJ, Murcia MA, Jimenez-Monreal AM, Tur JA, Bibiloni MM, Alonso GL, et al. Influence of diet in multiple sclerosis: A systematic review. Adv Nutr 2017; 8(3): 463-72.
10. Jahromi SR, Toghae M, Jahromi MJ, Aloosh M. Dietary pattern and risk of multiple sclerosis. Iran J Neurol 2012; 11(2): 47-53.
11. Mische LJ, Mowry EM. The evidence for dietary interventions and nutritional supplements as treatment options in multiple sclerosis: A review. Curr Treat Options Neurol 2018; 20(4): 8.
12. Mahan LK, Raymond JL. Krause's food and the nutrition care process. St. Louis, MO: Elsevier Health Sciences; 2016.
13. Sedaghat F, Jessri M, Behrooz M, Mirghotbi M, Rashidkhani B. Mediterranean diet adherence and risk of multiple sclerosis: A case-control study. Asia Pac J Clin Nutr 2016; 25(2): 377-84.
14. Demarin V, Lisak M, Morovic S. Mediterranean diet in healthy lifestyle and prevention of stroke. Acta Clin Croat 2011; 50(1): 67-77.
15. Materljan E, Materljan M, Materljan B, Vlacic H, Baricev-Novakovic Z, Sepcic J. Multiple sclerosis and cancers in Croatia--a possible protective role of the "Mediterranean diet". Coll Antropol 2009; 33(2): 539-45.
16. Herndon R. Multiple sclerosis clinical trials: Part 1□Basic Considerations. Int J MS Care 2001; 3(1): 6-12.
17. Briggs FBS, Thompson NR, Conway DS. Prognostic factors of disability in relapsing remitting multiple sclerosis. Mult Scler Relat Disord 2019; 30: 9-16.
18. Newsome SD, von GG, Shou H, Baynes M, Marasigan RER, Calabresi PA, et al. Longitudinal assessment of hand function in individuals with multiple sclerosis. Mult Scler Relat Disord 2019; 32: 107-13.
19. Abbasi M, Kordi YA, Poursadeghfard M, Parsaei JF, Motealleh A, Sobhani S. Whole body vibration improves core muscle strength and endurance in ambulant individuals with multiple sclerosis: A randomized clinical trial. Mult Scler Relat Disord 2019; 32: 88-93.
20. Yoon S, Noh JS, Choi SY, Baik JH. Effects of atypical antipsychotic drugs on body weight and food intake in dopamine D2 receptor knockout mice. Biochem Biophys Res Commun 2010; 393(2): 235-41.
21. Wang J, Hu M, Guo X, Wu R, Li L, Zhao J. Cognitive effects of atypical antipsychotic drugs in first-episode drug-naive schizophrenic patients. Neural Regen Res 2013; 8(3): 277-86.
22. Miller DD. Atypical antipsychotics: Sleep, sedation, and efficacy. Prim Care Companion J Clin Psychiatry 2004; 6(Suppl 2): 3-7.
23. Ghajarzadeh M, Jalilian R, Eskandari G, Ali SM, Reza AA. Validity and reliability of Persian version of Modified Fatigue Impact Scale (MFIS) questionnaire in Iranian patients with multiple sclerosis. Disabil Rehabil 2013; 35(18): 1509-12.
24. Eshaghi A, Riyahi-Alam S, Roostaei T, Haeri G, Aghsaei A, Aidi MR, et al. Validity and reliability of a Persian translation of the Minimal Assessment of Cognitive Function in Multiple Sclerosis (MACFIMS). Clin Neuropsychol 2012; 26(6): 975-84.
25. Morris G, Berk M, Walder K, Maes M. Central pathways causing fatigue in neuro-inflammatory and autoimmune illnesses. BMC Med 2015; 13: 28.
26. Wahls T, Scott MO, Alshare Z, Rubenstein L, Darling W, Carr L, et al. Dietary approaches to treat MS-related fatigue: comparing the modified Paleolithic (Wahls Elimination) and low saturated fat (Swank) diets on perceived fatigue in persons with relapsing-remitting multiple sclerosis: study protocol for a randomized controlled trial. Trials 2018; 19(1): 309.
27. Bonaccio M, Pounis G, Cerletti C, Donati MB, Iacoviello L, de Gaetano G. Mediterranean diet, dietary polyphenols and low grade inflammation: Results from the MOLI-SANI study. Br J Clin Pharmacol 2017; 83(1): 107-13.
28. Schwingshackl L, Hoffmann G. Mediterranean dietary pattern, inflammation and endothelial function: A systematic review and meta-analysis of intervention trials. Nutr Metab Cardiovasc Dis 2014; 24(9): 929-39.
29. Medina-Remon A, Casas R, Tressserra-Rimbau A, Ros E, Martinez-Gonzalez MA, Fito M, et al. Polyphenol intake from a Mediterranean diet decreases inflammatory biomarkers related to atherosclerosis: A substudy of the PREDIMED trial. Br J Clin Pharmacol 2017; 83(1): 114-28.
30. Sureda A, Bibiloni MDM, Julibert A, Bouzas C, Argelich E, Llompart I, et al. Adherence to the mediterranean diet and inflammatory markers. Nutrients 2018; 10(1): 62.
31. Yadav V, Marracci G, Kim E, Spain R, Cameron M, Overs S, et al. Low-fat, plant-based diet in multiple sclerosis: A randomized controlled trial. Mult Scler Relat Disord 2016; 9: 80-90.
32. Weiland TJ, Jelinek GA, Marck CH, Hadgkiss EJ, van der Meer DM, Pereira NG, et al. Clinically significant fatigue: Prevalence and associated factors in an international sample of adults with multiple sclerosis recruited via the internet. PLoS One 2015; 10(2): e0115541.
33. Francis HM, Stevenson RJ. Potential for diet to prevent and remediate cognitive deficits in neurological disorders. Nutr Rev 2018; 76(3): 204-17.
34. Feart C, Samieri C, Barberger-Gateau P. Mediterranean diet and cognitive health: an update of available knowledge. Curr Opin Clin Nutr Metab Care 2015; 18(1): 51-62.
35. Petersson SD, Philippou E. Mediterranean diet, cognitive function, and dementia: A systematic review of the evidence. Adv Nutr 2016; 7(5): 889-904.
36. Singh B, Parsaik AK, Mielke MM, Erwin PJ, Knopman DS, Petersen RC, et al. Association of Mediterranean diet with mild cognitive impairment and Alzheimer's disease: A systematic review and meta-analysis. J Alzheimers Dis 2014; 39(2): 271-82.
37. Feart C, Samieri C, Alles B, Barberger-Gateau P. Potential benefits of adherence to the Mediterranean diet on cognitive health. Proc Nutr Soc 2013; 72(1): 140-52.