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Diet and disease-related outcomes in multiple sclerosis: A systematic review of clinical trials

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Diet; Multiple Sclerosis; Systematic Review; Fatigue

Abstract

Background: A growing number of clinical trials have investigated the role of diet in multiple sclerosis (MS) patients. We systematically reviewed the literature for clinical trials to assess the impact of different kinds of diets on MS-related outcomes.

Methods: We searched MEDLINE, EMBASE, and Web of Science for relevant studies published before July 2019. The clinical trials included a defined dietary intervention and MS outcomes, including fatigue, relapse rate (RR), quality of life (QOL), and disability.

Results: In the present review, 15 trials on 669 MS patients were included. The 2 plant-based diet trials, 1 was low-fat and the other was low-calorie, included in the review showed a large effect (ES: 0.6 to 0.7) on fatigue compared to the regular diet. The other plant-based diet was a low-protein diet and showed moderate to large effects on disability and RR compared to the Western diet. Moreover, 2 studies showed the clinically meaningful effects of the ketogenic diet (KD) on QOL and disability compared to the regular diet. In addition, 2 studies compared fish oil (FO) to placebo and found a small effect on disability (ES: 0.1 to 0.3). There were 2 studies that evaluated evening primrose oil and hemp seed oil and showed medium to large effect (ES: 0.7 to 1.5) on RR compared to olive oil. Finally, we found 2 studies that showed high flavonoid cocoa had a moderate effect (ES: 0.4) on fatigue and a small effect (ES: 0.04) on QOL compared to low flavonoid cocoa.

Conclusion: Plant-based diet is a backbone for dietary recommendations in MS patients although low-fat, low-calorie, and KD diets with the addition of fish oil, vegetable oil, and flavonoids could be helpful.

Introduction

Multiple sclerosis (MS) is an immune-mediated, chronic inflammatory, and neurodegenerative disorder of the central nervous system (CNS) that results in physical and psychological disabilities.[1-3]

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These disabilities in young people with MS negatively impact the socio-economic condition of either the affected person or their families.[4,5]

Scientists emphasize that dietary recommendations are a principal part of the multifaceted therapy as the best choices for the treatment of MS because the available medicines alone have not been able to control MS progression and outcomes.[6-8] There are two considerable aspects in dietary recommendations that can reduce the disease progression trend in MS patients, one results in nutritional deficiency prevention, and the other results in following some specific diets that help MS treatment.[9,10]

In this way, some studies have shown that specific diets characterized by low fat, low calories, low protein, or rich in vegetables might regulate the immune system function and modulate the disease activity in MS patients.[11,12] In this study, we have systematically searched and reviewed the literature only for clinical trials that have assessed the effects of diets specific to the management of disease-related outcomes; however, we did not find enough evidence for definite recommendations.

Materials and Methods

Literature search: The authors provided a search strategy and searched MEDLINE (PubMed interface), EMBASE (OVID interface), and Web of Science using MeSH terms and keywords related to MS and diet according to supplementary file 1. Our search was limited to full articles and human studies in English without time limitations. Finally, the results were categorized using EndNote. The present study protocol is available in PROSPERO with the identifier code CRD42019144969.

Selection criteria: Only full English articles of clinical trials in patients with all types of MS were included in the present review. The control groups in the included studies could have received any type of placebo or diet.

Interventions included the following food components and dietary patterns:

Carbohydrates such as grains, beans, legumes, cereals, etc./Proteins such as egg, fish, red meat, etc./Fats such as olive oil, nuts, and fish oils, plant oils, etc./Fibers such as fruits and vegetables, etc./Beverages such as alcohol, coffee, tea, etc./Dairy products/and Dietary patterns (a composition of food groups), e.g. Ketogenic and plant-based diets, etc.

In addition, animal studies, reviews, letters or abstracts from conferences, observational studies, case reports, and articles focusing on children, pregnant, or lactating women were excluded. Moreover, studies with micronutrients or chemical product supplementation (e.g., vitamin D, iron, omega-3, and probiotics) were excluded. The eligible articles were determined by 2 independent authors (SB and EK) according to the mentioned inclusion and exclusion criteria, with a hierarchical strategy based on the screening of titles and abstracts in the first step and the screening of full texts in the second step (figure 1). All review articles were retained to avoid doing repetitious work.

Data extraction: Data, including general characteristics of included studies and disease-related outcomes, were extracted by 2 independent authors. General characteristics of studies included first author, year, country, size of samples at baseline and the end of the study, gender and age of patients, intervention duration, types of dietary interventions, and details of methods. The measured outcomes included disability, relapse rate, fatigue, and quality of life (QOL). The outcomes were possibly evaluated by the calculation of effect size (mean and 95% CI.) using Cohen's d test; d = 0.2, 0.5, and 0.8 are indicative of small, medium, and large effects, respectively.

Results

Search results: We found 4,073 articles on PubMed, 971 articles on Web of Science, and 418 articles on EMBASE, from among these, 906 articles were eliminated because of duplicated findings. After screening of titles and abstracts, 33 out of 4,556 publications were considered as eligible studies and 19 were excluded due to lack of a proper design (n = 9), lack of required data (n = 3), and lack of defined interventions (n = 7) (figure 1). Finally, we found 1 more article through hand searching of references in eligible studies. The general characteristics of the 15 included studies and 669 enrolled patients are presented in table 1. Moreover, the effects of dietary interventions on patients were extracted and are presented in table 2.

Plant-based diet: We detected 3 studies that assessed the effect of plant-based diets on MS patients (Table 1).[13-15] Yadav et al. investigated the effect of a low-fat, plant-based diet for 12 months characterized by consuming a high amount of fruits and vegetables, especially starchy vegetables (beans, potatoes, rice, pasta, and corn), and restricting animal products (eggs, dairy, fish, and meat) and vegetable oils.

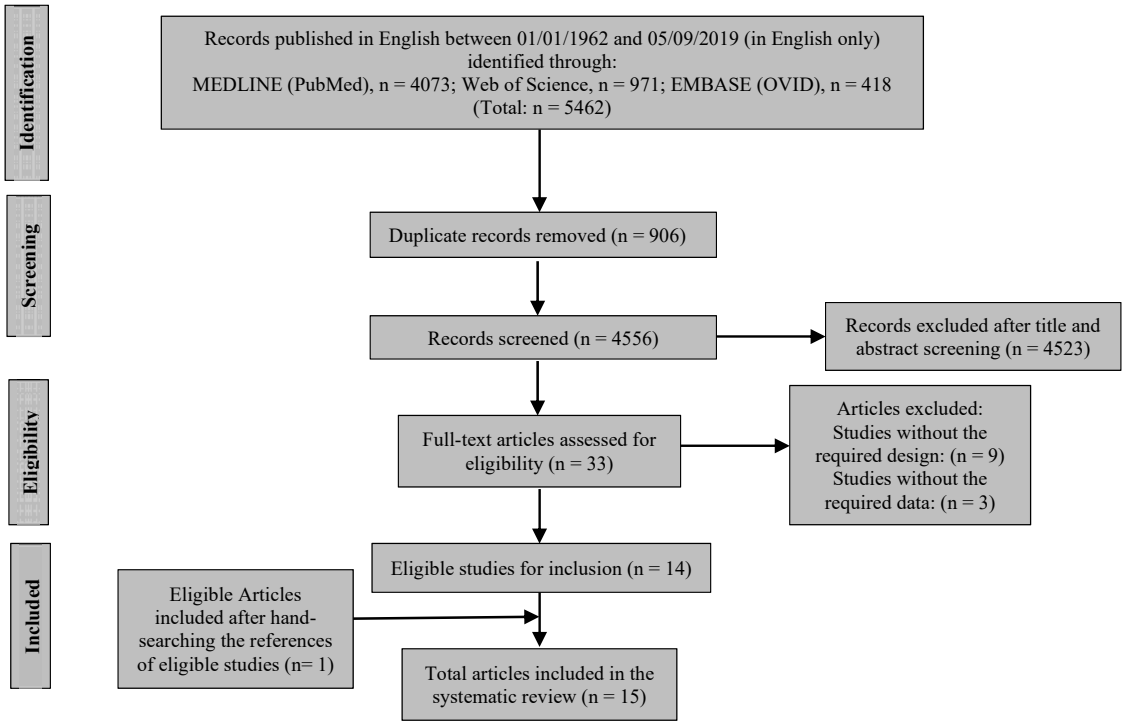

Figure 1: The flow diagram of the study

This diet meets the mean energy percentage of 10, 14, and 76 from fat, protein, and carbohydrate, respectively. It improved fatigue with medium to large effect size (P = 0.040, ES: -0.6 to -0.7) in MS patients compared to the usual diet in the control group. This dietary pattern could not significantly change disability, QOL, and physical function.[13]

The intervention in the study by Riccio et al. included a calorie-restricted and semi-vegetarian diet for 7 months characterized by a calorie intake of 1700-1800 kcal including 50% carbohydrate, 30% fat (mainly fish, olive, and vegetable oils), and 20% protein per day in comparison to a regular diet in the control group.[14] The diet included a high consumption of vegetables, fruits, nuts, fish, oysters, unrefined bread and pasta, soy, low-fat dairy products, olive oil, tea, and coffee. Alternately, there was low consumption of salt, sugar, animal fat, and red meat (once or twice a week), fried or processed foods (once every 2 weeks), cakes (once a week), alcohol (once a week), and no consumption of processed sweetened drinks and snacks. The diet showed no significant p-value for the variations in fatigue, QOL, and disability, but we calculated a medium to large effect in fatigue (ES: -0.78) and QOL (ES: -3.06) in MS patients.[14] Saresella et al. evaluated a 12-month diet described as high-vegetable and low-protein.[15] This was rich in fruits, vegetables, legumes, nuts, whole grains, and olive oil while it was poor in animal proteins including fish (twice a week), poultry (once a week), eggs (4 times a week), and dairy products (once a week). Patients limited the intake of refined grains, sugar, salt, fried foods, red meat, and saturated fats, while the control group followed a Western diet rich in red meats, refined grains, sweet or salty foods, and omega-6 or saturated fatty acids. The results showed a large effect on disability (P < 0.001, ES: -7.89), and relapse rate (RR) (P = 0.030, ES: 9.23) was reduced (Table 2).[15]

Ketogenic and fasting diets: Two articles that evaluated the efficacy of ketogenic and fasting diets in MS patients are available in table 1.[16,17] Choi et al. examined the effects of 2 dietary interventions, including the ketogenic diet (KD) and the fasting-mimic diet (FMD) in comparison with the German diet (GD) as the control group over a 6-month period in MS patients.[16] The KD group had a daily consumption of less than 50 grams of carbohydrates, less than 100 grams of proteins, and more than 160 grams of fats. Another group with the FMD diet followed a Mediterranean diet for 6 months after experiencing a 7-day fasting.[16]

Table 1. General characteristics of included studies and diet interventions

Author, Country	Study design	Disease course at enrollment	Number of participants in the: intervention & control groups at start/end of study	Mean age (SD): intervention & control groups (year)	Number of men/women in the intervention & control groups	Disease duration, mean (SD) or range: intervention & control groups (year)	Interventions & placebo	Mean duration of intervention (months)
Yadav et al., USA[13]	P* SB* RCT*	RRMS*	32/29 & 26/27	40.8 (8.86) & 40.9 (8.48)	31/1 & 26/3	5.33 (3.63) & 5.30 (3.86)	Intervention: Low-fat, plant-based diet + at least 30 min of moderate intensity activity on at least 5 days per week Control: Usual diet + at least 30 min of moderate intensity activity on at least 5 days per week	12
Riccio et al., Italy[14]	P RCT	RRMS PPMS*	11/10 & 11/10	NR*	10/1 & 8/2	NR	Intervention: Calorie-restricted and semi-vegetarian diet Control: Regular diet	7
Saresella et al., Italy[15]	P CT*	RRMS	10/10 & 10/10	42.3 (3.44) & 48.6 (6.02)	8/2 & 7/3	9.2 (9.4) & 11.5 (11.6)	Intervention: High-vegetable, low-protein diet Control: Western diet	12
Choi et al., USA[16]	P RCT	RRMS	20/20 & 18/12	44.4 (11.1) & 50.5 (10.4)	15/13 & 9/3	11 (7.7) & 9.9 (9.2)	Intervention: FMD* for 7 days followed by MD* for 6 months Control: Regular diet of the German population	6
Choi et al., USA[16]	P RCT	RRMS	20/20 & 18/12	41.3 (8.2) & 50.5 (10.4)	14/4 & 9/3	6.3 (4.3) & 9.9 (9.2)	Intervention: KD Control: Regular diet of the German population	6
Bock et al., Germany[17]	P RCT	RRMS	18/18/12 & 18/18/12	44.4 (11.1) & 41.3 (8.2) & 50.5 (10.4)	15/3 & 14/4 & 9/3	11 (7.7) & 6.3 (4.3) & 9.9 (9.2)	Intervention 1: PF* Intervention 2: KD Control: CD*	6
Irish et al., USA[18]	P RCT	RRMS	17/17 & 8/9	34.5 (5.7) & 37.1 (3.7)	7/1 & 8/1	NR	Intervention: MPDI* Control: Usual diet	3
Ramirez-Ramirez et al., Mexico[19]	P PC* DB* RCT	MS	25/25 & 20/19	35.1 (7.6) & 34.7 (7.8)	4/21 & 4/21	7.14 (4.79) & 6.68 (5.69)	Intervention: FO* capsules (4 g/day) containing 0.8 g EPA, 1.6 g DHA and excipient containing glycerin, purified water, tocopherol, sunflower oil, and titanium dioxide). Control: 4 g/day placebo containing glycerin, purified water, tocopherol, sunflower oil, and titanium dioxide	12
Torres-Sanchez et al., Mexico[20]	P DB RCT	RRMS	23/23 & 23/23	35.1 (7.6) (For all)	NR	7.1 (For all)	Intervention 1: FO capsules (4 g/day) containing 0.8 g EPA* and 1.6 g DHA* Intervention 2: OO capsules containing 1 g oleic acid	12

Table 1. General characteristics of included studies and diet interventions (continue)

Author, Country	Study design	Disease course at enrollment	Number of participants in the: intervention & control groups at start/end of study	Mean age (SD): intervention & control groups (year)	Number of men/women in the intervention & control groups	Disease duration, mean (SD) or range: intervention & control groups (year)	Interventions & placebo	Mean duration of intervention (months)
Weinstock-Guttman et al., USA[21]	PC P DB RCT	RRMS	15/16 & 13/14	39.9 (10) & 45.1 (7.7)	12/2 & 11/2	4.6 (3.5) & 6.9 (5.9)	Intervention 1: Low fat diet (15% fat) + FO (6 capsules per day; 1g* total) Intervention 2: Low cholesterol diet (< 30% fat and < 10 % saturated fat) + OO (6 capsules per day; 1 g total)	11 (2.9)
Zandi-Esfahan et al., Iran[22]	P PC DB RCT	RRMS	25/25 & 21/20	35.19 (9.97) & 31.40 (8.41)	13/12 & 16/9	NR	Intervention: One capsule per day containing 1 gr FO Control: Placebo capsule	12
Rezapour-Firouzi et al., Iran[23]	P DB RCT	RRMS	34/33/33 & 23/22/20	34.2 (7.5) & 35.9 (7.8) & 33.7 (7.8)	16/7 & 11/11 & 15/5	6.29 (3.9) & 7.55 (5.08) & 6.60 (4)	Intervention 1: 18-21 g/day of HSO* + EPO* + Hot-nature diet Intervention 2: 18-21 g/day of OO Intervention 3: 18-21 g/day of HSO +EPO	6
Majdinasab et al., Iran[24]	P PC DB RCT	RRMS	26/26 & 26/26	20–55 y/o & 20–55 y/o	20/6 & 18/8	1–5 & 1–5	Intervention: capsule containing 1 gr/day EPO Control: Placebo capsule	3
Adalat et al., Iran[25]	P PC DB RCT	MS	26/26 & 26/20	36.8 (7.4) & 35 (9)	20/6 & 16/4	7.1 (5.8) & 12 (5.6)	Intervention: Herbal extract syrup of saffron, cinnamon, St John's wort, and grapes Control: Herbal extract syrup of St John's wort and grape	1
Coe et al., UK[26]	CO* SB RCT	RRMS SPMS* PPMS	12/12 & 12/12	54 (10.56) (For all)	10/2 (For all)	15.21 (8.57) (For all)	Intervention: Cocoa with high flavonoid containing 350 mg gallic acid/g Control: Cocoa with low flavonoid containing 120 mg gallic acid/g	1 day
Coe et al., UK[27]	P PC DB, RCT	RRMS	19/21 & 19/19	41 (11) & 46 (8)	14/5 & 16/5	< 10 year diagnosis of MS (For all)	Intervention: High flavonoid cocoa powder mixed with heated rice Control: Low flavonoid cocoa powder mixed with heated rice	1.4

G: group; NS: Not Significant; EDSS: Expanded Disability Status Scale; MSFC: Multiple Sclerosis Functional Composite; RR: Relapse Rate; MFIS: Modified Fatigue Impact Scale; QOL: Quality of life; SF-36: Short Form 36 Health Survey Questionnaire; MHI: Mental Health Inventory; FSS: Fatigue Severity Scale; Neuro-QOL: Neurology Quality-of-Life; 6MWT: 6 Min Walk Test; VAS: Visual Analog Scale; MS-54: Multiple Sclerosis Quality of Life 54; FMD: Fasting Mimicking Diet; KD: Ketogenic Diet; CD: Control Diet; T25FW: The Timed 25 Foot Walk; 9HPT: 9-Hole PEG Test; PASAT: Paced Audio Serial Addition Test; WD: Western Diet; HV/LP: High vegetable/ Low protein; PF: Prolonged Fasting diet; MHI: Mental Health Inventory; PCS: Physical Component Scale; Im: Immeasurable according to reported data

Table 2. Disease related outcomes and main conclusions

Author, Country	Outcome measures used	P, effect size, and conclusion
Yadav et al., USA[13]	1) Fatigue: a) FSS* b) MFIS* 2) Relapse: RR* 3) Disability: a) EDSS* b) MSFC* 4) QOL*: SF-36	FSS: Intervention G: decreased by 0.06 points per month/ Control G: increased by 0.18 points per month/ P-value of differences between the two groups: 0.06/ ES: -0.66: medium to large MFIS: Intervention G: decreased by 0.23 points per month/ Control G: increased by 0.43 points per month/ P-value of differences between the two groups: 0.04/ ES: -0.70: medium to large RR*: Change in intervention G: 0.37/ Change in control G: 0.47/ P-value of differences between the two groups: 0.56/ ES: 0.16: Small MSFC: P-value of differences between the two groups: NS/ ES: Im EDSS: P-value of differences between the two groups: NS/ ES: Im SF-36, Mental: P-value of differences between the two groups: NS/ ES: Im SF-36, Physical: P-value of differences between the two groups: NS/ ES: Im Conclusion: This diet resulted in moderate improvement in fatigue in MS patients.
Riccio et al., Italy[14]	1) Disability: EDSS 2) Fatigue: FSS 3) QOL: FS-36	EDSS: Intervention G: baseline: 1.91 (1.44 to 2.38) / after: 1.91 (1.44 to 2.38)/ Control G: baseline: 1.8 (1.29 to 2.31)/ after: 1.8 (1.29 to 2.31)/ P: NS/ ES: 0 FSS: Intervention G: baseline: 30.09 (3.79 to 56.4)/ after: 29.91 (22.6 to 37.2)/ Control G: baseline: 23.4 (14.1 to 32.7) / after: 25.9 (15.5 to 36.3)/ P < 0.050/ ES: -0.78: medium to large FS-36: Intervention G: baseline: 100.18 (93.6 to 107) / after: 98.73 (93 to 104)/ Control G: baseline: 103 (99 to 107) / after: 105.1 (101 to 109)/ P: NS/ ES: -3.06: large Conclusion: Although, EDSS, FSS, and QOL did not change significantly after the intervention in the present study, the diet showed a medium to large effect on fatigue and QOL in MS patients.
Saresella et al., Italy[15]	1) Disability: EDSS 2) Relapse: RR	EDSS: Intervention G: baseline: 1.7 (1.33 to 2.07) / after: 1 (1 to 1), (P = 0.060)/ Control G: baseline: 2.16 (1.47 to 2.85)/ after: 2.53 (2.05 to 3.01), (P = 0.310)/ P-value of differences between the two groups: (P = 0.001)/ ES: -7.89: large RR: Intervention G: baseline: 0.66 (0.127 to 1.19) / after: 0.33 (-0.203 to 0.863), (P = 0.600)/ Control G: baseline: 0.46 (0.193 to 0.727)/ after: 1 (1 to 1), (P = 0.040)/ P-value of differences between the two groups: (P = 0.030)/ ES: -9.23: large Conclusions: This diet improved clinical parameters including disability and relapse in MS patients with a large ES.
Choi et al., USA[16]	1) QOL: MS-54 2) Disability: EDSS	QOL: P-value of differences between the two groups after 6 months: < 0.005/ Increase of ≥ 5 points are considered as clinically important at month 3/ showed clinically meaningful improvement on MS-54 scores, after 3 months: ES: 0.4 to 0.5: medium to large EDSS: P-value of differences between the two groups after 6 months: < 0.05/ ES: -0.63: medium to large Conclusion: This study detected a medium to large reduction in EDSS in the FMD and KD groups compared to the German diet (measured on Day 7 for FMD and Day 30 for KD) in MS patients.
Choi et al., USA[16]	1) QOL: MS-54 2) Disability: EDSS	QOL: P-value of differences between the two groups after 3 and 6 months: < 0.005/ After 6 months: ES: 0.3 to 0.5: medium to large EDSS: P-value of differences between the two groups after 6 months: < 0.01/ ES: -0.39: medium Conclusion: A medium reduction was observed in EDSS in the FMD and KD groups (measured on Day 7 for FMD and Day 30 for KD) in MS patients.
Bock et al., Germany[17]	QOL: MS-54	QOL: threshold is thought to be a clinically meaningful gain (> 5 points) in MS-54 outcome: In PF compared to control at month 3: ES: 0.8: medium to large In KD compared to control at month 6: ES: 0.7: medium to large Conclusion: This study showed that PF and KD induce a medium to large effect on QOL in MS patients.

Table 2. Disease related outcomes and main conclusions (continue)

Author, Country	Outcome measures used	P, effect size, and conclusion
Irish et al., USA[18]	1) Fatigue: FSS 2) Disability: MFSC a) Upper motor function: 9HPT* b) Lower motor function: T25FW* c) Cognitive function: PASAT* 3) QOL: MS-54 a) QOL-mental b) QOL-physical	FSS: Change in intervention G: decreased by 1.4 points/ Change in control G: increased by 0.2 points, P-value between changes of two groups: 0.03/ ES: Im 9HPT: Change in intervention G: decreased by 15.1% and 18.2% for the dominant and non-dominant hand, respectably/ Change in control G: decreased by 3% and 7.4% for the dominant and non-dominant hand, respectably. P-value of differences between the two groups in the dominant hand: 0.02 and non-dominant hand: 0.05/ ES: Im T25FW time: Change in intervention G: improved by 11.6%/ Change in control G: improved by 3%/ P-value between changes of two groups: 0.09/ ES: Im PASAT: Change in intervention G: improved by 10.9%/ Change in control G: improved by 5.5%/ P-value between changes of two groups: 0.17: NS/ ES: Im QOL-m: Change in intervention G: improved by 16.2%/ Change in control G: decreased by 1.5%/ P-value between changes of two groups: 0.02/ ES: Im QOL-p: P-value of differences between the two groups: 0.03/ ES: Im Conclusion: A Paleolithic diet may be useful in the treatment and management of MS through reducing fatigue, and increasing mental and physical QOL.
Ramirez-Ramirez et al., Mexico[19]	1) Disability: EDSS 2) Relapse: RR	EDSS: Change in intervention G: 0.1 (0.3)/ Change in control G: 0.2 (0.26)/ P-value between changes of two groups: 0.66/ ES: -0.36: medium RR: Intervention G: after: 0.84 (0.9)/ Control G: after: 1 (1)/ P-value of differences between the two groups: 0.79/ ES: Im Conclusion: Fish oil could be effective on EDSS with a medium ES; however; a significant p-value was not achieved in MS patients.
Torres-Sanchez et al., Mexico[20]	Disability: EDSS	EDSS: P-value of differences between the two groups: NS/ ES: Im Conclusion: Fish oil was not significantly effective on EDSS in MS patients.
Weinstock-Guttman et al., USA[21]	1) Disability: a) EDSS b) MSFC 2) Relapse: RR 3) Fatigue: MFIS* 4) QOL* (SF-36*): a) MHI* b) PCS*	EDSS: Change in FO: decreased by 0.07/ Change in OO: increased or worsening by 0.35/ ES: Im RR: Change in FO: -0.79(-1.4 to -0.181): (P = 0.020) / Change in OO: -0.69 (-1.29 to -0.087): (P = 0.040)/ ES: -0.09: small MFIS: P-value of differences between the two groups after 6 months: 0.03 and after 12 months: 0.05 (Favoring OO)/ ES: Im MHI: P-value of differences between the two groups after 6 months (increased in FO): 0.05: NS/ ES: Im PCS: P-value of differences between the two groups after 6 months (increased in FO): 0.05: NS/ ES: Im Conclusion: This study suggested that a low-fat diet supplemented with fish oil could have a moderate effect in MS patients.
Zandi-Esfahan et al., Iran[22]	Disability: EDSS	EDSS: Intervention G: baseline: 3.10 (2.55 to 3.65), after: 2.30 (1.92 to 2.68)/ Control G: baseline: 2.55 (1.94 to 3.15), after: 1.68 (1.17 to 2.19)/ P-value of differences between the two groups: (P = 0.080)/ ES: -0.10: small Conclusion: There was no statistically significant difference in EDSS between the groups in MS patients.
Rezapour-Firouzi et al., Iran[23]	1) Disability: EDSS 2) Relapse: RR	EDSS: Intervention G 1: baseline: 2.76 (2.19 to 3.33)/ after: 1.77 (1.08 to 2.46): P = 0.001 Intervention G 2: baseline: 3.54 (2.95 to 4.13)/ after: 1.41 (-0.2 to 3.02): P = 0.005 Intervention G 3: baseline: 3.25 (2.4 to 4.1)/ after: 1.83 (0.54 to 3.12): P = 0.002 ES between G1&G2: 1.51: large ES between G3&G2: 0.74: medium to large RR: Intervention G 1: baseline: 0.31 (0.22 to 0.39)/ after: 0.04 (-0.04 to 0.12): P = 0.001 Intervention G 2: baseline: 0.38 (0.17 to 0.58)/ after: 0.18 (0.01 to 0.34): P = 0.050

Table 2. Disease related outcomes and main conclusions (continue)

Author, Country	Outcome measures used	P, Effect size, and Conclusion
Rezapour-Firouzi et al., Iran[23]	1) Disability: EDSS 2) Relapse: RR	Intervention G 3: baseline: 0.43 (0.255 to 0.605)/ after: 0.05 (-0.0464 to 0.146): (P = 0.002) ES between G1&G2: -0.70: medium to large ES between G3&G2: -1.55: large Conclusion: In MS patients, the combination of HSO and EPO as a dietary supplement in a daily dose of 18-21 g/day over a period of 6 months showed immune-modulating effects in significant improvements of the relapse rate compared to a control group receiving 18-21 g olive oil per day. Note: The calculated ES for EDSS in our study did not match the article conclusion because we found that all of the interventions could reduce EDSS significantly, but OO could improve that with medium to large ES in comparison to HSO and EPO, but this study conclusion was reported inversely.
Majdinasab et al., Iran[24]	1) QOL: a) Cognitive function b) Overall life satisfaction 2) Fatigue: MFIS	Overall life satisfaction: Intervention G: baseline: 67.11, after: 75.94- Control G: baseline: 65.24, after: 66.52/ P-value of differences between the two groups: <0.001/ ES: Im Cognitive function: Intervention G: baseline: 53.08, after: 69.42, Control G: baseline: 62.11, after: 62.5/ P-value of differences between the two groups: <0.001/ ES: Im MFIS: Intervention G: baseline: 32.08, after: 11.96/ Control G: baseline: 24.42, after: 20.69/ P-value of differences between the two groups: <0.001/ ES: Im Conclusion: This study indicated that EPO consumption had no impact on the QOL in general; however, it had a significant effect on several aspects of QOL such as the cognitive function and overall life satisfaction. In addition, it had a significant effect on fatigue in MS patients.
Adalat et al., Iran[25]	1) Fatigue: a) FSS b) MFIS	FSS: Change in intervention G: -19.8/ Change in control G: -4.6/ P < 0.001/ ES: -1.57: large MFIS: Change in intervention G: -19.7/ Change in control G: -3.5/ P < 0.001)/ ES: -2.27: large Conclusion: The present study suggests that herbal extract may improve fatigue symptoms with a large ES in MS patients.
Coe et al., UK[26]	1) Fatigue: VAS 2) Physical activity	VAS*: ES: 0.32: medium Physical activity: ES: 0.47: medium Conclusion: A moderate effect was observed on fatigue throughout the day in favor of the high flavonoid group in MS patients.
Coe et al., UK[27]	Fatigue: Neuro-QoL	Neuro-QoL: ES: 0.04: small Conclusion: High flavonoid intake demonstrates a small potential to improve fatigue in MS patients in this study.

G: group; NS: Not Significant; EDSS: Expanded Disability Status Scale; MSFC: Multiple Sclerosis Functional Composite; RR: Relapse Rate; MFIS: Modified Fatigue Impact Scale; QOL: Quality of life; SF-36: Short Form 36 Health Survey Questionnaire; MHI: Mental Health Inventory; FSS: Fatigue Severity Scale; Neuro-QOL: Neurology Quality-of-Life; 6MWT: 6 Min Walk Test; VAS: Visual Analog Scale; MS-54: Multiple Sclerosis Quality of Life 54; FMD: Fasting Mimicking Diet; KD: Ketogenic Diet; CD: Control Diet; T25FW: The Timed 25 Foot Walk; 9HPT: 9-Hole PEG Test; PASAT: Paced Audio Serial Addition Test; WD: Western Diet; HV/LP: High vegetable/ Low protein; PF: Prolonged Fasting diet; MHI: Mental Health Inventory; PCS: Physical Component Scale; Im: Immeasurable according to reported data

The GD is characterized by a lower intake of vegetables, and higher consumption of meats, cereals, fruits, beer, dairy products, and fats.[28] Finally, the study showed the beneficial effect of the KD on QOL after 3 and 6 months (P < 0.005, ES: 0.3-0.5). Disability decreased in both KD (P < 0.010) and FMD groups in comparison to the control group with moderate to large effect size (P < 0.050, ES: -0.3 to -0.6).[16]

Bock et al. compared the impact of prolonged fasting (PF) or KD in MS patients with the usual diet as the control group.[17] There were several stages of the PF diet, including a 2-day low-calorie vegetarian diet, 7-day intensive fasting (vegetable with 200-350 kcal), a 3-day low-calorie vegetarian diet, and one, every day, week-long, 14-hour per day fast for the remaining study period. The PF and KD meaningfully affected QOL with large ES (ES: 0.7 to 0.8) (Table 2).[17]

Modified Paleolithic diet: We found one study that investigated the modified Paleolithic diet (MPD) in MS patients (Tables 1 and 2).[19] The MPD is a diet rich in vegetables and fruits (9 cups per day) and nuts while it is poor in legumes, dairy products, sugar, processed foods, oils, and foods containing gluten such as grains, and includes a moderate intake of meats. Irish et al. compared the effects of MPD with the usual American diet (UAD) as the control group.[18] The UAD consists of low intake of fruits, vegetables, dairy, oils, and high saturated fats, sugar, and sodium. This diet pattern meets or exceeds the recommended intake of grains and protein foods.[29] The study revealed that adherence to MPD, compared to UAD, improved fatigue (P = 0.030), mental QOL (P = 0.020), physical QOL (P = 0.030), and upper motor function as a subset of disability test (P for the dominant hand = 0.02 and P for the non-dominant hand = 0.05) (Table 2).[18]

Fish oil: We found 4 studies that determined the effects of fish oil (FO) in MS patients (Table 1).[19-22] The study by Ramirez-Ramirez et al. showed that a 12-month intervention with 4 grams of FO per day [containing 1.6 g Docosahexaenoic acid (DHA) and 0.8 g Eicosapentaenoic acid (EPA)] could not significantly change disability (P = 0.600) and RR (P = 0.700) in MS patients, [19] but it has a medium effect size on disability. Torres-Sanchez et al. compared the effects of 4 grams of FO (containing 1.6 g DHA and 0.8 g EPA) and 4 grams of olive oil (OO) for 12 months in MS patients and reported no significant changes.[20]

Weinstock-Guttman et al. compared the effects of a 12-month FO intervention with OO in MS patients. One group received FO (1.32 g DHA and 1.98 g EPA) accompanied by a low-fat and low-saturated fatty asids (low-SFAs) dietary pattern (calorie intake from lipids < 15%), and another group received OO (1 g oleic acid) accompanied by a dietary pattern based on guidelines of the American Heart Association (AHA). The AHA guideline recommends a low-cholesterol dietary pattern with less than 10% calorie intake from SFA and about 30% from total fat.[21] The study showed that physical QOL and mental health had improved in the FO group in comparison to the OO group (P = 0.050 for both) after 6 months, but this trend was close to that in the OO group after 12 months. In addition, RR was reduced in response to both the OO (P = 0.040) and FO (P = 0.020), but FO had a small effect compared to OO. However, fatigue had reduced in the OO group (P = 0.050) compared to the FO group, and disability had insignificantly decreased in the FO group (Table 2).[21] Zandi-Esfahan et al. reported that 1 gram of fish oil (containing 120 mg DHA and 180 mg EPA) caused no significant improvement in disability (P = 0.080, ES: 0.1) (Table 2).[22]

Vegetable oils: Four studies have shown the effects of vegetable oils including OO, evening primrose oil (EPO), and hemp seed oil (HSO) on MS outcomes [20,21,23,24] 2 of which have been described in the previous section (Table 1).[20,21]

Rezapour-Firouzi et al. designed a trial including 3 groups of MS patients to investigate the impact of HSO and EPO.[23] The first group received a diet rich in hot-natured foods supplemented with combined HSO and EPO (18-21 g) every day, the second group received OO (18-21 g) every day, and the third group received combined HSO and EPO (18-21 g) every day for 6 months. Disability and RR reduced in the first (P = 0.001 for both) and third groups (P = 0.002 for both) after the intervention compared to before the intervention. In addition, in the OO group, RR and disability significantly reduced (P = 0.005),[23] but HSO and EPO induced a larger effect on RR compared to OO (ES: 0.7-1.5).

Majdinasab et al. showed that 3-month supplementation with EPO (1 gram per day) could improve fatigue and QOL (P < 0.001 for all) compared to the placebo group (Table 2).[24] The study showed that HSO and EPO decreased inflammatory cytokines and increased anti-inflammatory cytokines in MS patients.[23] The sterols and tocopherols present in both HSO and

EPO may prevent oxidation and help alleviate MS outcomes. Gamma-linolenic acid (GLA) is Omega-6 fatty acid.[30,31] Di-homo-gamma-linolenic acid (DGLA) derives from GLA and is known as a protective factor against inflammation due to its prostaglandin E2 reducing effect.[32]

Furthermore, monounsaturated fatty acids such as oleic acid and polyphenols existing in OO can prevent lipid peroxidation and ATP-synthesize enzyme oxidation, induce greater fluidity in the membrane, and higher performance of the mitochondria, and thus, may regulate the immune system function, and consequently, reduce RR and fatigue in MS patients.[33-36]

Studies have shown the beneficial effects of EPO in the treatment of diseases such as diabetes and rheumatoid arthritis.[37-40] EPO is an excellent source of 3 terpene ester derivatives that scavenge free radicals, and prevent cyclooxygenase and neutrophil elastase activities, and thereby, improve inflammation status.[41]

Traditional diet: Traditional therapies classify all foods into cold-natured and hot-natured, and recommend a balanced eating for the maintenance of health.[42] Moreover, people have a dominant basic temper called Mizaj, which is thought to influence mental and physical functions.[43]

The hot-natured diet is a dietary pattern characterized by high intake of hot-natured foods and low intake of cold-natured foods. Hot-natured foods include wheat and soy products, eggs, domestic poultry and turkey, garlic, onion, and carrots, cantaloupe, grape, coconut and banana, olive oil, sesame oil, honey, nuts, and spices such as turmeric, mustard, and cinnamon. Furthermore, cold-natured foods include rice, potato, corn, junk foods, beef, fish, solid fats, vegetables such as cucumber and spinach, fruits such as watermelon and citrus, carbonated soft drinks, and beer.[23] Scientists believe that there is a strong association between a hot-natured diet and regulation of the immune system function.[44]

The herbal syrup used in the study by Adalat et al.[25] included saffron that is a well-known herb and includes crocin, picrocrocin, and safranal, which have antioxidant, anti-inflammatory, and neuroprotective properties through their inhibiting effects on cyclooxygenase activity and leukocytes filtration.[45-48] St John's wort has hyperforin, which possesses antioxidant, anti-inflammatory, and anti-depressant properties due to its elevation of serotonin and noradrenaline in the brain.[49-52]

Turmeric extract has demonstrated a promoting effect on sodium benzoate formation in the liver. Due to the effect of sodium benzoate on the modulation of the immune system function, maintenance of blood-brain barrier integration, and myelin production, turmeric might prevent the progression of MS.[53-55] Many researches have shown that the components presented in grape contain proanthocyanidins, anthocyanins, and resveratrol, which have anti-inflammatory properties.[56-60]

Flavonoids: Flavonoids can diminish oxidative stress, and increase glucose availability and blood flow to the brain, which improve fatigue and physical activity.[61-63] Finally, we recommend fruits and vegetables rich in flavonoids such as onions, kale, grapes, and berries for MS patients.

Conclusion

Clinical evidence has shown that following a suitable diet as a complementary therapy is necessary in MS patients. Our review showed that plant-based diets could be a central core for dietary recommendations. On the other hand, following low-fat, low-calorie, and low-protein plant-based diets for a long time induce nutritional deficiencies due to the limitations in the intake of some kinds of food groups such as dairy and grains. Thus, we recommend that MS patients correct plant-based diets with moderate intakes of some foods such as fish, poultry, and low-fat dairy to prevent the side effects of these diets. FMD and KD are useful in MS, but hard to tolerate for a long time because of their side effects such as disturbing the lipid profile and inducing some nutritional deficiencies. There is not enough evidence for a conclusion to be made about traditional dietary factors and a hot-natured diet on MS. We believe that further studies are required to identify the effects and side effects of these diets in MS.

Limitations: Because of the large heterogeneity of the entered studies including type of MS, type and duration of diets as interventions, etc., we could not pool the data and perform a meta-analysis in this study.

Conflict of Interests

The authors declare no conflict of interest in this study.

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