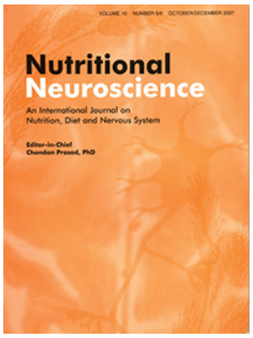

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Effects of different dietary interventions in multiple sclerosis: a systematic review of evidence from 2018 to 2022

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Effects of different dietary interventions in multiple sclerosis: a systematic review of evidence from 2018 to 2022

Büşra Atabilen and Yasemin Akdevelioğlu

Department of Nutrition and Dietetics, Faculty of Health Sciences, Gazi University, Ankara 06490, Turkey

ABSTRACT

Background: Nutrition is an important risk factor for both Multiple sclerosis (MS) development and post-diagnosis disease prognosis. However, it is important to evaluate the diet as a whole instead of considering the effects of nutrients individually.

Aims: In this systematic review, it was aimed to evaluate the effect of different dietary interventions in MS patients and to determine the most appropriate dietary model for this group.

Methods: The search was carried out between February 2022 and March 2022 in three different databases, 'PubMed', 'Web of Science' and 'The Cochrane Library' over the university access network. After the search for the determined keywords, a total of 269 studies conducted between 2018 and 2022 were identified, but only 17 of them were found to be suitable for inclusion criteria.

Results and conclusion: Although there are studies reporting positive health outcomes for energy-restricted/intermittent fasting diets, ketogenic diet, and modified paleolithic diet, these diets may not be applicable diets in the long-term as they may cause deficiencies of various nutrients. No current study was found for low-fat diets, gluten-free diet and Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diet applied to individuals with MS. The Mediterranean diet, on the other hand, is more recommendable than other diet models due to the positive health results reported in long-term studies and the absence of any side effects. However, more studies are needed to reach a definite conclusion.

KEYWORDS

Multiple sclerosis; Mediterranean diet; MIND diet; intermittent fasting; low-fat diets; ketogenic diet; Wahls diet; Gluten-free diet

1. Introduction

Multiple sclerosis (MS) is an immune-mediated disease characterized by demyelination and axonal loss affecting the central nervous system. It can often lead to severe physical or cognitive impairment and neurological problems in young adults [1]. Although the cause is unknown in MS pathology; research shows that genetic, immunological, and environmental factors may all play a role in a complex etiology [1, 2]. However, inflammation that occurs when exposed to risk factors is one of the most important factors in the development of the disease [1]. When examined in terms of nutritional risk factors, it was reported for the first time in the 1950s that the restriction of saturated fatty acids led to an improvement in the clinical condition and an increase in the quality of life in MS patients. Other than saturated fatty acids, a high-energy western-style diet, red meat, high sodium intake, and high consumption of added sugars are among the other nutrition-related risk factors that are important in the development of MS [3].

It may be a more correct approach to consider the diet as a whole rather than individually evaluating the effects of nutrients in disease development and progression. The effects of different dietary patterns on disease symptoms or quality of life is one of the issues that has been evaluated recently in MS patients [4]. Patients may turn to different diet models as an alternative or complementary treatment option, especially after the diagnosis of MS. However, preferred diets may not always be healthy options. Individuals with MS have an increased risk of cardiometabolic comorbidity, and this situation is associated with worse MS-related outcomes, thus it is important to emphasize a healthy diet pattern in this population [5].

2. Methods

This systematic review aims to evaluate the effect of different dietary interventions in MS patients and to determine the most appropriate dietary model for this group. The systematic compilation question was determined as follows:

CONTACT Büşra Atabilen busra.atbln@hotmail.com Department of Nutrition and Dietetics, Faculty of Health Sciences, Gazi University, Emek Neighborhood Bişkek Street, 6th Street (Former 81st Street), Ankara 06490, Turkey

- Do different dietary interventions have an impact on disease-related symptoms or disease prognosis in individuals with MS?

This review was written according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) criteria [6]. The preliminary protocol of the review has been uploaded to the PROSPERO database. The search was carried out between January 2022 and February 2022 in three different databases: 'PubMed', 'Web of Science', and 'The Cochrane Library' over the university's access network. Searching in these databases was carried out using < fasting mimicking diet, intermittent fasting, calorie restriction, weight loss diet, ketogenic diet, modified Atkins diet, paleolithic diet, modified paleolithic diet, Wahls diet, Wahls elimination diet, low-fat diet, Swank diet, McDougall diet, gluten-free diet, Mediterranean diet, modified Mediterranean diet, MIND diet>, 'and' <multiple sclerosis > keywords. Only clinical, randomized controlled, cross-sectional, or prospective human studies were included. Case reports, reviews, and meta-analyses were excluded. In addition, only written in English and studies from the last five years were included. Studies conducted outside of adults (infant, adolescent) were excluded. The flow chart of the study is given in Figure 1. In addition, the components of the diets evaluated in the systematic review are shown in Table 1.

3. Results and discussion

3.1. Calorie restricted/intermittent fasting diets

One of the most important risk factors associated with the etiology of MS is obesity [12]. Obesity, particularly in adolescence and early adulthood, has been reported to be associated with an increased risk of developing pediatric and adult MS [13]. Changes in microbiota composition in obese individuals may affect immune and inflammatory functions and lead to the development of MS. In addition, the increased leptin level in obesity can affect the inflammatory process and stimulate the development of the disease [12]. Therefore, weight management is an important issue in obese individuals. Calorie restriction or intermittent fasting diets, which have become popular recently, can often be applied in weight management. Intermittent fasting diets are an emerging unconventional approach to achieving bodyweight loss and improving metabolic health beyond calorie-restricted diets [14]. There are different intermittent fasting diet models associated with fasting-satiety cycles, meal timing, and energy intake. The alternate fasting diet (5:2) is a diet model in which 25% or less of the energy requirement is taken two days a week and no restrictions are made on other days. In a time-restricted diet, food intake is restricted to 8 h or less each day. On the other hand, in the periodic fasting diet, it is possible to fast for up to 24 h once or twice a week, and to continue normal food intake on other days [15, 16].

Studies in which calorie restriction or intermittent fasting diets were applied in individuals with MS are summarized in Table 2. In a study in which traditional calorie restriction was performed, patients with MS were given a diet containing 200–350 kcal/day of energy for 7 days. At the end of the study, no significant change was found in the serum neurofilament light chain (NfL) level, which is a proposed biomarker in the evaluation of prognosis in MS [17]. In a pilot study in which 36 individuals with MS were randomized to traditional calorie restriction (22% restriction in energy intake), intermittent fasting diet (75% restriction in energy intake 2 days a week), or a control diet for 8 weeks, greater weight loss occurred in the calorie-restricted group. Although the adherence rate to the intermittent fasting diet was lower than the traditional calorie restriction group, significant improvements were noted in terms of emotional well-being and depression scores in both the calorie-restricted group and the intermittent fasting group [18]. In another similarly planned study, there was a significant decrease in memory T cells in the group of the intermittent fasting diet, while there was no change in the traditional calorie-restricted group or the control group [19]. In addition to studies comparing traditional calorie restriction and intermittent fasting diets, in a pilot clinical study examining the effect of intermittent fasting diets alone, it was shown that intermittent fasting diets can create protective changes in serum adipokine levels and microbiota in individuals with MS [20].

Traditional calorie-restricted diets or intermittent fasting diets have been reported to be safe in individuals with MS [21]. In particular, intermittent fasting diets may have positive effects on health in individuals with MS, by regulating circadian biology by reducing nighttime eating behavior, their effects on changeable lifestyle behaviors such as sleep or regulating gut microbiota [22]. In addition, the shift of energy metabolism from carbohydrates to fatty acids and ketone bodies during fasting and satiety periods can make cells and organs resistant to oxidative stress and improve the antioxidant defense system [23]. However, diets in which energy intake is severely restricted or intermittent fasting diets are not viable long-term diets, and their long-term effects are unknown. In addition, symptoms such as weakness, fatigue, and headache due to the restriction

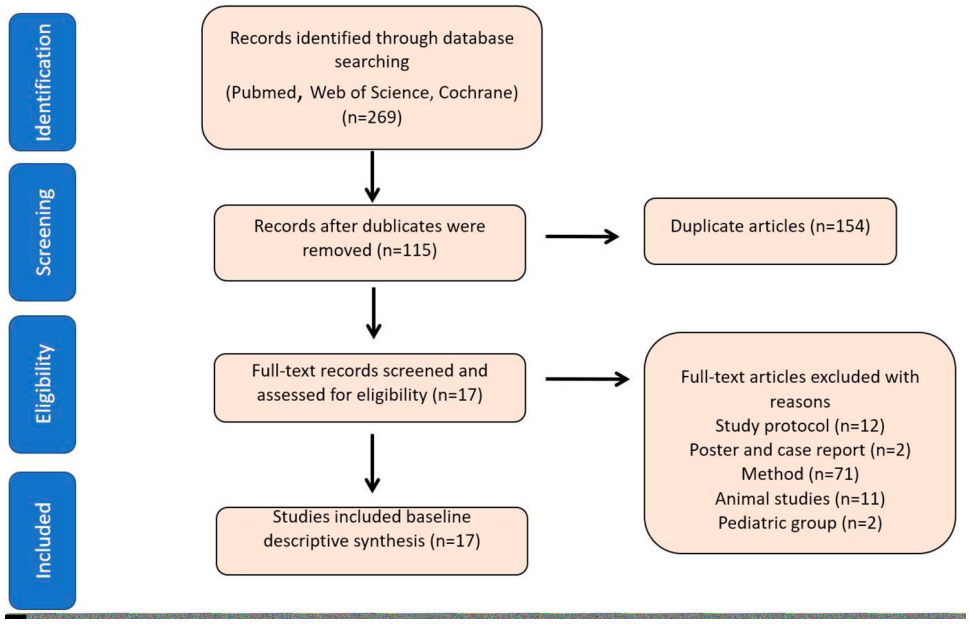

Figure 1. Systematic review flow chart.

of energy intake may worsen the existing condition in patients with MS [24]. Especially in women, decreased bone mineral density and menstrual irregularities may occur [4].

3.2. Ketogenic diet

The ketogenic diet is a high-fat, moderate-protein, and very low-carb diet. Decreased insulin secretion and depletion of glycogen stores due to carbohydrate intake below 50 g stimulate the transition to the metabolic processes of gluconeogenesis and ketogenesis [25]. It is thought that this change in the metabolic process and increased ketone bodies may provide bodyweight loss, reduce inflammation, and increase antioxidant capacity. For this reason, there are studies on the use of ketogenic diets, which were initially used in the treatment of epilepsy, obesity, and many neurodegenerative diseases [26].

The effects of the ketogenic diet in individuals with MS are given in Table 3. Studies have shown that a ketogenic diet can improve fatigue and depression scores [27], and decrease pro-inflammatory enzyme (ALOX5) gene expression [28]. Speech and voice-related problems may occur in 50–60% of individuals with MS. In a study planned for this purpose, it was reported that the ketogenic diet may cause a significant improvement in the voice handicap index score in individuals with speech and voice problems [29]. In a study in which individuals were followed on a ketogenic diet (40% carbohydrate, 20% protein, 40% fat) for 4 months, a significant increase in lean tissue mass, perception of satiety, and paraoxonase 1 (PON1) enzyme level was reported [30]. However, in the criticism published for this study, it was stated that 40% carbohydrate was high, and 40% fat was low for the ketogenic diet [31]. In addition to studies reporting positive results of ketogenic diets, there is also a study showing that the ketogenic diet has no clinical effects [7].

The clinical effect of the ketogenic diet in individuals with MS is due to its potential regulatory role in anti-inflammatory pathways. The increase in ketone bodies after a ketogenic diet may stimulate oxidative stress resistance genes by regulating epigenetic mechanisms. Increased levels of ketone bodies, adenosine, and polyunsaturated fatty acids can inhibit the inflammatory process through various pathways. In addition, the ketogenic diet's direct reduction in reactive oxygen species (ROS) production and its regulatory effect on the microbiota also provide a neuroprotective effect (Figure 2) [32, 33]. However, although the available evidence indicates that ketogenic diets do not cause serious safety concerns, more studies are needed to evaluate the long-term effects in the clinic due to the low quality of studies, short duration, and small sample size [34, 35].

3.3. Modified paleolithic diet (Wahls diet)

The Paleolithic diet is the modern interpretation of the 'Paleolithic' or 'Old Stone Age' diet. The basic principle of this diet is based on returning to the diet of our prehistoric ancestors and rejecting today's eating habits to

Table 1. Description of the diets.

Food	MCT-based ketogenic diet [7]	Modified paleolithic diet (Wahls diet) [7]	Wahls elimination diet [8, 9]	Swank diet [8, 9]	Mediterranean diet [10]	MIND diet [11]
Green leafy vegetables	2–3 servings/day	3 servings/day	>2–3 servings/day	No suggestion	No suggestion	≥6 servings/week
Sulfur-rich vegetables	2–3 servings/day	3 servings/day	>2–3 servings/day	No suggestion	No suggestion	No suggestion
Intensely colored fruits or vegetables	2–3 servings/day	3 servings/day	>2–3 servings/day	>2 servings/day vegetables >2 servings/day fruits	1-2 servings fruits in every main meal ≥2 servings vegetables in every main meal	≥1 serving/day other vegetables ≥2 servings/week berries
Fish	16 ounces/week	16 ounces/week	16 ounces/week	≤ 1.75 ounces (50 g) fatty fish/day	≥2 servings/week	≥1 serving/week
Red meat	6–12 ounces all meat/day	6–12 ounces all meat/day	As desired	Not allowed	<2 servings/week	<4 servings/week
Poultry	6–12 ounces all meat/day	6–12 ounces all meat/day	As desired	Dark meat and skin not allowed	2 servings/week	≥2 servings/week
Organ meat	12 ounces/week	12 ounces/week	12 ounces/week	Not allowed	Not allowed	Not allowed
Legumes	Avoid	As desired	Not allowed	Allowed if low saturated fat	Recommended in every day	≥3 servings/week
Nuts and seeds	Max 4 ounces-soaked nuts/day	Max 4 ounces-soaked nuts/day	Maximum 4 ounces/day, soaked and rinsed	Allowed in limited amounts	1–2 servings/day	≥5 servings/week
Olive oil	As desired *Recommended; 4–5 tablespoons coconut oil per day	As desired	As desired	*4–10 teaspoons (20–50 g) unsaturated oil/day	Recommended in every main meal	As primary plant oil
Grains	Not allowed	2 servings/week gluten-free grains	Not allowed	4 ounces/day (preferably whole grains)	1–2 servings in every main meal (preferably whole grains)	≥3 servings/day (preferably whole grains)
Dairy	Recommended; full fat coconut milk only	Not allowed	Not allowed	2 cups/day skim or fat-free only	2 servings/day	<1 ounce serving/week cheese
Eggs	Not allowed	Not allowed	Not allowed	Whole eggs ≤1/day, ≤ 3/week; egg whites as desired	2–4 servings/week	No suggestion

improve health [36]. Therefore, this diet mostly includes organ meats, meat, fish, fruits, and root vegetables in accordance with the conditions of the Paleolithic period. Consumption of milk and dairy products, cereals, legumes, and processed foods is prohibited [37]. The modified paleolithic diet or Wahls diet, developed by Dr. Terry Wahls based on traditional paleolithic diet principles, does not contain eggs and dairy products, allows the consumption of gluten-free grains twice a week, recommends consumption of nine + cups of fruit and vegetables a day and consumption of seaweed and the use of saturated fats in meals, and limit animal protein intake. Although the Wahls Diet has a low glycemic index, it also contains low amounts of certain nutrients [38]. Due to insufficient intake of some nutrients, nutritional supplements are recommended for individuals. However, after nutritional supplementation, there is a concern that the upper limit may be exceeded, especially for vitamin D and niacin [39, 40]. After the Wahls diet, the Wahls Elimination diet was developed in 2015, which eliminated gluten-free grains and legumes from the diet. The Wahls Elimination diet was created with a low lectin content as lectin increases intestinal permeability and activates immune system cells [9].

The effects of the modified paleolithic diet in individuals with MS are summarized in Table 4. According to the results of the studies, a significant decrease in fatigue scale [7, 8, 41], improvement in quality of life scale score [41], and improvement in lipid profile [8] were shown in MS patients followed by a modified paleolithic diet/Wahls diet. However, although the results of the studies show that the Wahls diet may have positive effects on clinical findings in MS patients, the number of studies is quite insufficient to draw a general conclusion. The Wahls diet is not viable in the long term as it is a diet that recommends excluding foods containing important nutrients such as egg, dairy products, cereals, and supplementing against the risk of nutrient deficiency. In addition, nutritional supplements in the Wahls diet may have positively affected the results of the studies.

3.4. Low-fat diets (Swank and McDougall diet)

The Swank diet was first proposed as a treatment option by Dr. Roy Swank in the 1950s. In this diet model,

Table 2. Effects of calorie-restricted/intermittent fasting diets in individuals with multiple sclerosis.

	Study group	Method	Study outputs	Results	Reference
① Fitzgerald et al, 2018	36 patients diagnosed with MS between the ages of 18–50 years	Study period: 8 weeks Randomization into three groups: (1) Traditional calorie restriction (22% restriction in energy intake), (2) Intermittent fasting diet (75% restriction in energy intake 2 days a week) (3) Control group	Weight loss and mood change	→Greater weight loss in the group with the traditional calorie restriction →Adherence to the intermittent fasting diet was lower than the calorie restriction group →Significant improvements in emotional well-being and depression scores in both the calorie-restricted and the intermittent fasting group	[18]
② Cignarella et al, 2018	16 patients diagnosed with MS	Study period: 15 days Randomization into two groups: (1) Intermittent fasting diet (<500 kcal/day every other day) (2) Control group	Serum adiponectin, leptin, blood immune cells, microbiota analysis	→Although the leptin level decreased in both groups, it was higher in the intermittent fasting diet group →Adiponectin levels increased in both groups, with no significant difference between groups →While absolute T and B lymphocyte cells increased in the control group, they decreased or remained stable in the intermittent fasting diet group →*Faecalibacterium, Lachnospiracea Incertae sedis* and *Blautia* showed an increasing trend after 15 days of intermittent fasting diet, with no significant difference between groups	[20]
③ Roman et al, 2020	70 patients diagnosed with relapsing-remitting MS	Three pilot studies: First study period: 48 weeks →One group was given an energy-restricted diet (22% restriction in energy intake), and the other group was given an intermittent fasting diet (75% restriction in energy intake 2 days a week) Second study period: 24 weeks →Individuals were included in the energy-restricted diet (22% restriction in energy intake) or intermittent fasting diet (75% restriction in energy intake 2 days a week) group according to their preferences. Third study period: 24 weeks →Individuals were included in the time-restricted diet (food consumption in 8 h of the day) or the control group.	Feasibility/Adherence, safety, and patient-reported outcomes	→Energy-restricted diets and intermittent fasting diets are safe for MS patients →Adherence to a time-restricted diet is higher than an energy-restricted diet →No significant change was noted in patient-reported results (fatigue, sleep, and quality of life)	[21]
④ Bock et al, 2022	40 patients diagnosed with MS	Study period: 6 months Randomization into three groups: (1) Calorie restricted diet (200-350 kcal/day for the first 7 days, then isocaloric diet) (n = 14) (2) Modified ketogenic diet (<50 g carbohydrates, > 160 g fat, and protein intake ≤100 g per day) (n = 17) (3) Control group (n = 9)	Serum neurofilament light chain (NfL) level	→A decrease in serum neurofilament light chain (NfL) level after 6 months in the modified ketogenic diet group →There was no change in the group that received a calorie-restricted diet for 7 days	[17]
⑤ Fitzgerald et al, 2022	36 patients diagnosed with MS between the ages of 18–50 years	Study period: 8 weeks Randomization into three groups: (1) Traditional calorie restriction (22% restriction in energy intake), (2) Intermittent fasting diet (75% restriction in energy intake 2 days a week) (3) Control group	T cells	→Significant decrease in memory t cells in the intermittent fasting diet group	[19]

saturated fat intake is limited to <15 g/day and unsaturated fat intake to <40 g/day [42]. The reason for limiting fat is the thought that high fat intake will contribute to the progression of the disease in susceptible individuals [43]. High-fat diets may affect the development and prognosis of the disease by enhance autoimmune inflammation. In addition, high fat diets can lead to obesity, cardiovascular disease, hyperlipidemia, and type 2 diabetes, which could negatively impact MS prognosis [4].

Table 3. Effects of ketogenic diet in individuals with multiple sclerosis.

	Study group	Method	Study outputs	Results	Reference
① Bock et al, 2018	60 individuals diagnosed with relapsing-remitting MS	Study period: 6 months Randomization into three groups: (1) Calorie restricted diet (200-350 kcal/day for the first 7 days) (2) Modified ketogenic diet (<50 g carbohydrates, > 160 g fat, and protein intake ≤100 g per day) (3) Control group	Pro-inflammatory (ALOX5, COX1, COX2) and anti-inflammatory enzymes (ALOX15)	→Reduction in ALOX5 gene expression in the ketogenic diet group compared to the control group	[28]
② Brenton et al, 2019	20 patients diagnosed with relapsing-remitting MS	Study period: 6 months Individuals on a modified Atkins diet (<20 g carbohydrates) were followed. Study-specific parameters were evaluated at baseline and end.	Anthropometric measurements, fatigue and depression scale, and biochemical parameters	→75% of individuals completed the study →Body mass index and body fat percentage decreased significantly →Significant improvements were noted in depression and fatigue scale scores →Significant decrease in serum insulin, HbA1c and triglyceride levels, but the change in serum leptin and adiponectin levels is not significant	[27]
③ Benlloch et al, 2019	27 patients diagnosed with MS	Study period: 4 months Individuals on a ketogenic diet (40% carbohydrate, 20% protein, and 40% fat) were followed. Study-specific parameters were evaluated at baseline and end.	Anthropometric measurements, perception of satiety, beta-hydroxybutyrate, paraoxonase-1 (PON1), and ghrelin	→Significantly higher perception of satiety after lunch and dinner →Significant increase in lean tissue mass →Significant increase in PON1 level	[30]
④ Fidan et al, 2021	65 individuals diagnosed with MS with speech and voice-related problems	Study period: 3 months Randomization into two groups: (1) Ketogenic diet (n = 32) (2) Control group (n = 33)	Voice Handicap index	→Significant improvement in Voice Handicap index parameters in the ketogenic diet group	[29]
⑤ Lee et al, 2021	15 patients diagnosed with MS	Study period: 3 months Randomization into three groups: (1) Modified paleolithic diet (n = 6) (2) MCT-based ketogenic diet (70% fat) (n = 5) (3) Control group (n = 4)	Disability, fatigue, quality of life scale, cognitive and functional assessment	→Significant decrease in fatigue scale scores in those on the modified paleo diet compared to the control group →No significant change in clinical outcome in the ketogenic diet group	[7]

One of the most important concerns in individuals following the Swank diet is the occurrence of nutrient deficiencies. In a related study, it was reported that nutrient deficiencies other than fiber, potassium, and choline did not occur in those who consumed the Swank diet supplemented with cod liver oil, vitamin E, and multivitamin/mineral compared to a healthy diet model [43]. In another study, it was stated that dietary supplementation may cause excessive intake of vitamin D, niacin, and magnesium while preventing some nutrient deficiencies [40]. There is only one recent study examining the clinical effects of the Swank diet in individuals with MS. As mentioned earlier under the title of Wahls diet, a significant improvement was noted in fatigue scale scores in individuals with MS who followed the Swank diet [8]. However, more studies are needed to examine the long-term effectiveness of the Swank diet.

Another low-fat diet is the McDougall diet. While this diet is rich in starch-containing plant foods (legumes, bread, corn, rice, potatoes, fruits, and vegetables), it is a diet suitable for vegan eating habits as it does not include meat, fish, eggs, and dairy products. In the McDougall diet, about 10% of the energy comes from fat, 14% from protein, and 76% from carbohydrates [44]. There is no current study examining the clinical effects of the McDougall diet model in MS patients. However, when evaluated in terms of general dietary guidelines, removing foods of animal origin from the diet may cause nutrient deficiencies. Since fat is one of the most important nutrients that give taste to the diet, restricting fat in the diet may affect the taste and adeptness of the diet. In addition, due to the high fiber content of the diet, undesirable gastrointestinal side effects (bloating, gas, etc.) may occur in individuals.

3.5. Gluten-free diet

Increased immune system activation in autoimmune diseases may increase the likelihood of developing another autoimmune disease [45]. In particular, gluten

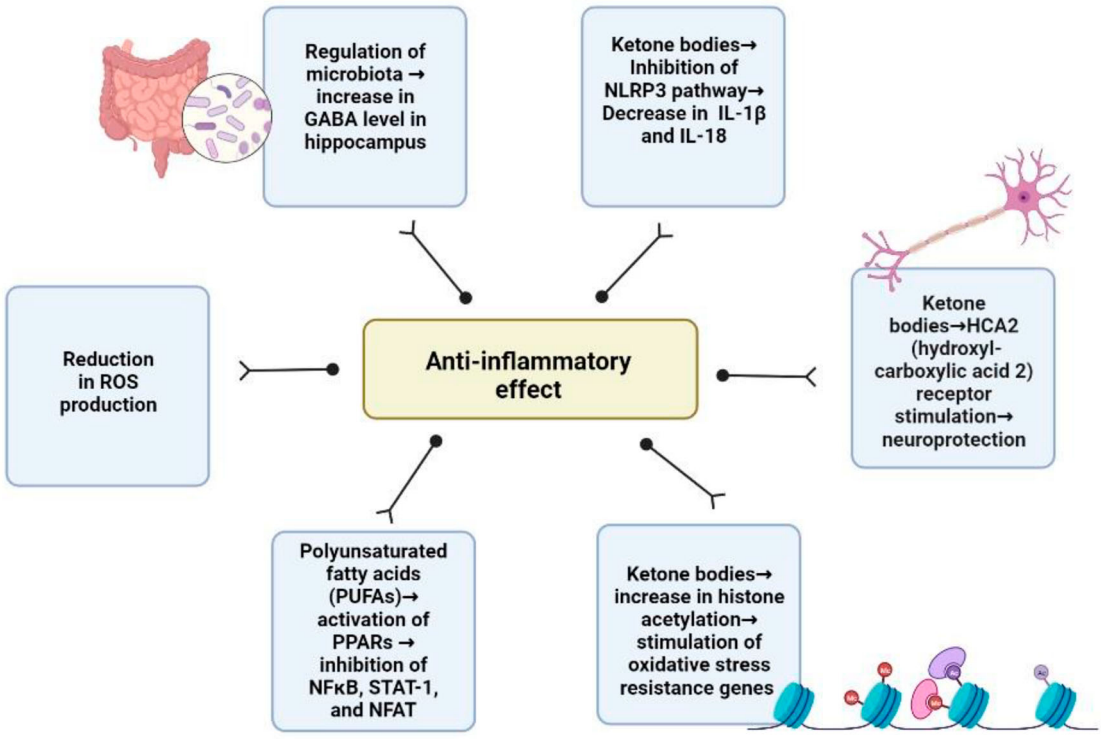

Figure 2. Anti-inflammatory mechanisms of action of the ketogenic diet [27, 28]. By regulating the microbiota, the ketogenic diet increases the level of the neurotransmitter GABA in the hippocampus, and decreases the production of reactive oxygen species. Long-chain fatty acids, which are among the ketogenic diet components, and the increased level of ketone bodies after ketogenic diet consumption can inhibit various pathways associated with inflammation. In addition, ketone bodies play a protective role against oxidative stress by increasing histone acetylation. (GABA: Gamma aminobutyric acid; NLRP3: NLR family pyrin domain containing 3; IL: interleukin; PPARs: Peroxisome proliferator-activated receptors; NF-κB: Nuclear factor kappa B; STAT-1: Signal transducer and activator of transcription 1; NFAT: Nuclear factor of activated T-cells.)

is a nutritional component that can be associated with other autoimmune diseases besides celiac disease through immune system activation [46]. Several mechanisms have been proposed in relation to gluten's role in neurodegenerative diseases in susceptible individuals. These include the following:

- Intestinal transglutaminase-2 (tTG2) is an enzyme that mediates the deamidation of glutamine residues found in gluten proteins. In addition, since it stimulates the production of tTG2 autoantibodies, it acts as an autoantigen and can stimulate the inflammatory response.
- By increasing intestinal permeability, it can cause toxic metabolites, bacteria, and bacterial toxins to reach the central nervous system through the blood. Disruption of the blood–brain barrier integrity can activate microglial cells and stimulate neuronal inflammation.
- Changes in the intestinal microbiota may lead to the development of neurodegenerative diseases through disruption in the microbiota-gut-brain axis [47].

Although antibodies suggestive of gluten intolerance are found to be elevated in individuals with MS, more studies are needed to clarify whether this is a result of two co-existing autoimmune diseases or a non-specific antibody response caused by an impaired immune system. However, since the gluten-related antibody level is found to be higher in MS patients with gastrointestinal complaints, it is thought that investigating the celiac risk in these patients may be beneficial [45]. Although gluten-free diet intervention in previous years has been shown to improve EDSS scores, MRI-defined lesion activity, fatigue, and quality of life scores in patients with MS, the number of studies is insufficient to draw a definitive conclusion [48]. In addition, there is no current study on the clinical effect of a gluten-free diet intervention in MS patients.

Gluten-free diets have recently become popular for a variety of reasons, including improving gastrointestinal symptoms or the perception that gluten is potentially harmful; thus, restriction represents a healthy lifestyle. However, excluding celiac, non-celiac gluten sensitivity, gluten-sensitive irritable bowel syndrome, and schizophrenia, the use of gluten-free diets is thought to be

Table 4. Effects of the modified paleolithic diet in individuals with multiple sclerosis.

	Study group	Method	Study outputs	Results	Reference
① Fellows et al, 2019	18 patients diagnosed with progressive MS	Study period: 12 months Individuals were followed by a modified paleolithic diet. Fish oil, B group vitamins, nutritional supplements to increase mitochondrial performance, and amino acid supplements have also been recommended to participants.	Fatigue Severity Scale (FSS) and lipid profile	→FSS score decreased significantly compared to baseline. →While HDL-cholesterol levels increased significantly compared to baseline; LDL-cholesterol and triglyceride levels significantly decreased.	[41]
② Lee et al, 2021	15 patients diagnosed with MS	Study period: 3 months Randomization into three groups: (1) Modified paleolithic diet (n = 6) (2) MCT-based ketogenic diet (70% fat) (n = 5) (3) Control group (n = 4)	Disability, fatigue, quality of life scale, cognitive and functional assessment	→Significant decrease in fatigue scale scores in those on the modified paleo diet compared to the control group →No significant change in clinical outcome in the ketogenic diet group	[7]
③ Wahls et al, 2021	87 patients diagnosed with relapsing-remitting MS	Study period: 24 weeks Randomization into two groups: (1) Wahls diet (n = 44) (2) Swank diet (n = 43)	Fatigue Severity Scale (FSS), Modified Fatigue Impact Scale (MFIS), Multiple Sclerosis Quality of Life-54 (MSQoL-54), and the 6-minute walk test	→35 patients from the Wahls diet group and 37 patients from the Swank diet group completed the study →Significant reduction in FSS and MFIS scores in both Swank and Wahls diet groups →Both physical and mental MSQoL scores improved significantly on the Wahl diet, while only the physical MSQoL score improved on the Swank diet group →No significant change in the 6-minute walk test in both groups	[8]

associated with negative effects rather than positive effects on health [49]. In addition, the European Society for Clinical Nutrition and Metabolism (ESPEN) does not recommend a gluten-free diet to prevent MS [50]. Therefore, the gluten-free diet can be applied in MS patients with celiac, non-celiac gluten sensitivity, gluten-sensitive irritable bowel syndrome, or schizophrenia, but more studies are needed to apply it in other situations.

3.6. Mediterranean diet

The Mediterranean diet is a diet model that recommends daily consumption of whole grains and legumes, fresh vegetables and fruits, moderate fish, small amounts of dairy products (especially – yoghurt and cheese), red meat and meat products consumption, and only a small amount of red wine at meals and olive oil and oilseeds as a source of fat [51]. Evidence shows that the Mediterranean diet has positive health effects and can improve quality of life [52]. The effects of the Mediterranean diet on health are mostly based on its lipid-lowering effect, protection against oxidative stress, inflammation and platelet aggregation, regulation of hormones and growth factors that play a role in cancer development, and the effect of metabolites mediated by the intestinal microbiota [53]. Figure 3 summarizes the neurological effects of the Mediterranean diet.

Studies examining the effect of the Mediterranean diet on individuals with MS can be divided into two groups in terms of method. In studies evaluating the adaptation of individuals to the Mediterranean diet without any dietary intervention (studies outside the scope of this systematic review), a significant negative relationship between MS severity score, EDSS score [54], and a decrease in the risk of central nervous system demyelination [55, 56] were reported in MS patients with high adherence to the Mediterranean diet. In addition, the Mediterranean diet was associated with a lower number of attacks [57]. Current studies examining the effects of dietary intervention following the method of our systematic review are shown in Table 5. In these studies, it was shown that the Mediterranean diet was associated with a significant improvement in the fatigue scale score [58–60] and an increase in quality of life [58]. It was also noted in a study that the Mediterranean diet caused a decrease in the level of interleukin-6 (IL-6) [61]. However, in some studies, epigallocatechin gallate and coconut oil supplementation [61] or a multidimensional rehabilitation program [62] in addition to the Mediterranean diet intervention may have affected the study results.

The positive effects of the Mediterranean diet in individuals with MS may be because antioxidant nutrients reduce oxidative stress and inflammation. In addition, the recommendation for the consumption of prebiotic

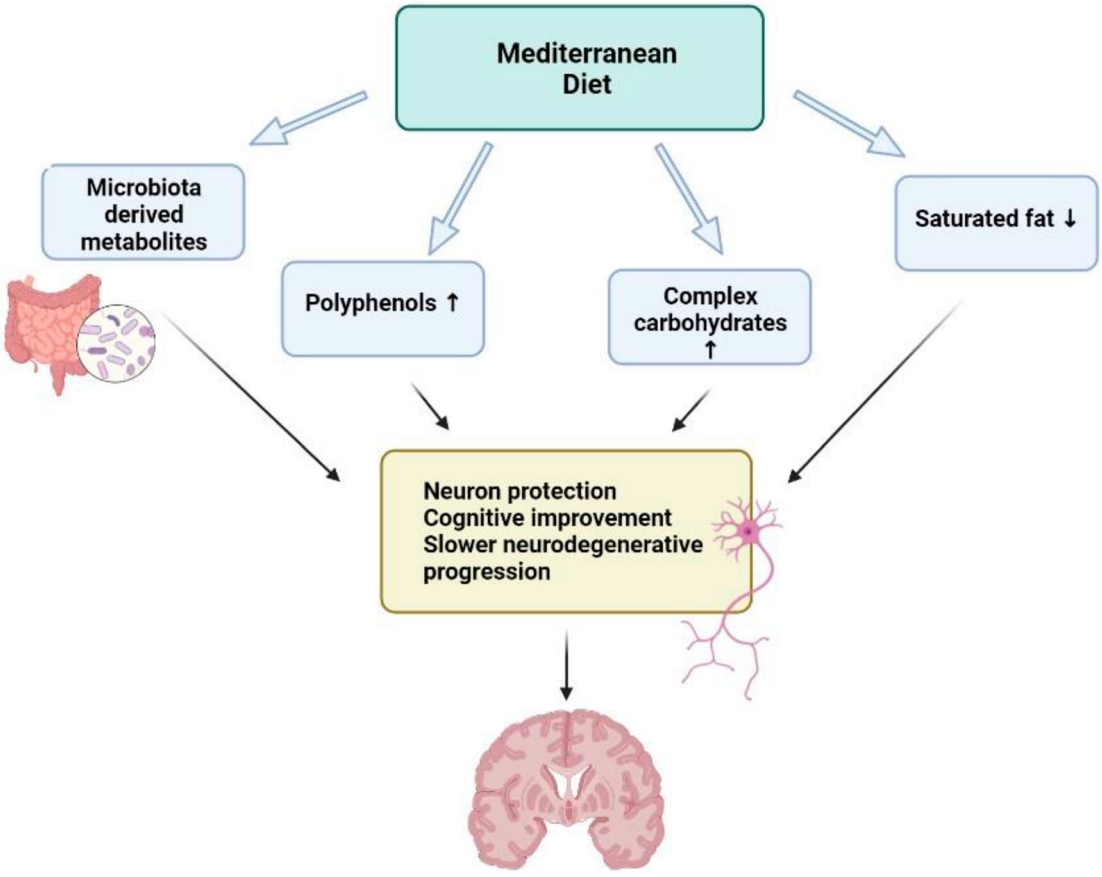

Figure 3. Neurological effects of the Mediterranean diet [48, 51]. The Mediterranean diet is rich in complex carbohydrates, polyphenols, and low in saturated fat. Indigestible dietary components in diets are also converted into health-beneficial metabolites by the gut microbiota. Therefore, a Mediterranean diet is important in neuron protection, cognitive improvement, and slows down the neurodegenerative progression.

foods in the Mediterranean diet may reduce intestinal inflammation and provide neurological protection through the production of biogenic amines. Finally, adherence to the Mediterranean diet limits the consumption of foods associated with the risk of developing MS [58]. A review examining the effect of different dietary patterns on MS also presented a higher level of evidence for the Mediterranean diet, and no adverse effects were reported [4].

3.7. Mediterranean-DASH intervention for neurodegenerative delay (MIND) diet

In recent years, the MIND (Mediterranean-DASH Intervention for the Neurodegenerative Delay) diet, which combines Mediterranean and dietary approaches to stop hypertension (DASH) diet guidelines, has been recommended as a diet model that is important in preventing the development of neurodegenerative diseases, has positive effects on cognitive function, and reduces the risk of depression [63–66]. Unlike the Mediterranean diet, the MIND diet emphasizes the consumption of berries and green leafy vegetables, and states that cheese consumption should be limited [11, 67].

Considering that depression may develop in almost half of MS patients [68] and cognitive functions may be adversely affected [69], it is estimated that the MIND diet model may have positive effects on the progression of the disease in these patients. However, there is no study on the MIND dietary intervention in MS patients. Only one study has shown that individuals with a high MIND diet adherence score have a lower risk of developing MS [70].

4. Conclusion and recommendations

In conclusion, in this systematic review, it was aimed to evaluate the effects of different dietary interventions in individuals with MS based on current study results. No current study was found for low-fat diets, gluten-free diets, and MIND diets applied to individuals with MS.

Table 5. Effects of the Mediterranean diet in individuals with multiple sclerosis.

	Study group	Method	Study outputs	Results	Reference
① Sand et al, 2019	36 women diagnosed with MS	Study period: 6 months Randomization into two groups: (1) Modified Mediterranean diet (exclusion of meat and dairy products, limitation of sodium intake to <2g/day) (n = 18) (2) Control group (no dietary intervention) (n = 18)	Expanded Disability Status Scale (EDSS), Multiple Sclerosis Functional Composite (MSFC), The Neurological Fatigue Index-MS, Multiple Sclerosis Impact Scale-29, Multiple Sclerosis Quality of Life-54	→ A significant decrease was reported in the Neurological Fatigue Index-MS, Multiple Sclerosis Impact Scale-29, and EDSS scores in the intervention group compared to the control group	[60]
② Moravejolahkami et al, 2020	180 patients diagnosed with relapsing-remitting MS	Study period: 6 months Randomization into two groups: (1) Modified Mediterranean diet (Changes have been made according to Iranian culture) (n = 68) (2) Traditional Iranian diet (n = 79)	Multiple Sclerosis Quality of Life-54 items, Fatigue Severity Scale (FSS-9), and Visual Analog Fatigue Scale	→A significant improvement in the quality-of-life scale score and a significant decrease in the fatigue scale score were reported in the modified Mediterranean diet group compared to the control group	[58]
③ Razeghi-Johromi et al, 2020	34 patients diagnosed with MS and 38 healthy control group	Study period: 1 year Randomization into two groups: (1) Modified Mediterranean diet (Red wine and some foods omitted according to Iranian culture) (2) Control diet (according to healthy eating recommendations)	Modified Fatigue Impact Scale and Minimal Assessment of Cognitive Function in MS	→ The fatigue score was significantly lower in the Mediterranean diet group → No significant improvement in cognitive status	[59]
④ Platero et al, 2020	51 patients diagnosed with MS	Study period: 4 months Randomization into two groups: (1) Intervention group (800 mg Epigallocatechin gallate and 60 mL coconut oil) (2) Control group (placebo) Both groups on the isocaloric Mediterranean diet were followed.	State-Trait Anxiety Inventory (STAI), IL-6 and EDSS	→ Decreased state anxiety and functional capacity in the intervention group →The interleukin-6 level decreased in both study groups	[61]
⑤ Barone et al, 2021	14 patients diagnosed with MS	Individuals were followed up with a 1-week multidimensional rehabilitation program (Neuromotor rehabilitation, Mediterranean diet, sailing course, and mindfulness)	Microbiota analysis, biochemical markers, MFIS-5, 6MWT-meters	→Improvement in microbiota dysbiosis →Decrease in proinflammatory lymphocyte and lipopolysaccharide levels →Reduction in fatigue scale	[62]

Although studies are reporting positive health outcomes for energy-restricted/intermittent fasting diets, ketogenic diets, and modified paleolithic diets, the studies are not sufficient to draw a definite conclusion in this patient group. In addition, these diets may not be applicable in the long term as they may cause deficiencies of various nutrients and may worsen the existing clinical situation by causing deficiencies. While the European Society for Clinical Nutrition and Metabolism (ESPEN) recommends a diet low in saturated fatty acids and rich in polyunsaturated fatty acids in individuals with MS (level of evidence B), it does not recommend n-3 fatty acids, vitamin B_{12}, and vitamin C supplementation to prevent MS [50]. In addition, the National Multiple Sclerosis Society (NMSS) states that there is no definitive diet that has been scientifically proven to be beneficial in MS. However, experts give the following recommendations: prepare meals at home whenever possible, include colorful fresh vegetables and fruits in your diet, choose whole grains, and avoid processed foods and added sugars [71].

Considering the NMSS and ESPEN recommendations, especially the Mediterranean diet is more recommendable than other diet models due to the positive health results reported in long-term studies and the absence of any side effects. Although the MIND diet, which is a diet model that combines the Mediterranean and DASH diet guidelines, is another healthy diet model, there are not enough study results to give a recommendation.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Data availability statements

The data that support the findings of this study are available from the corresponding author, [BA], upon reasonable request.

Notes on contributors

Büşra Atabilen works as a research assistant in the Gazi University, Faculty of Health Sciences, Department of Nutrition and Dietetics. Medical nutrition therapy in diseases, enteral and parenteral nutrition are among her area of expertise.

Yasemin Akdevelioğlu is a professor at Gazi University, Faculty of Health Sciences, Department of Nutrition and Dietetics. Nutritional biochemistry, reproductive health and nutrition are among her area of expertise.

ORCID

Büşra Atabilen http://orcid.org/0000-0002-8485-1763
Yasemin Akdevelioğlu http://orcid.org/0000-0002-2213-4419

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