REVIEW ARTICLE

Adv Psychiatry Neurol 2022; 31 (3): 128-137
DOI: https://doi.org/10.5114/ppn.2022.121730

Macronutrients, vitamins and minerals in the diet of multiple sclerosis patients

Correspondence to:

Magdalena Zielińska
Institute of Health Sciences
College of Medical Sciences
University of Rzeszow
35-959 Rzeszow, Poland
e-mail: mazielinska@ur.edu.pl

Submitted: 06.08.2022
Accepted: 17.10.2022

Magdalena Zielińska, Izabela Michońska

Institute of Health Sciences, College of Medical Sciences, University of Rzeszow, Poland

Abstract

Purpose: Multiple sclerosis (MS) is a chronic demyelinating disease of the central nervous system in which multifocal damage to the brain and spinal cord occurs. The etiology of MS remains unclear but it is often recognized by researchers as a multifactorial disease that involves autoimmune and genetic predisposition combined with environmental influences (e.g., low vitamin D levels, smoking, obesity). An adequate and balanced diet can be extremely helpful in improving the condition of MS patients, effectively supporting pharmacological therapy. The purpose of the study was to investigate whether, and if so, to what extent, the intake of macronutrients, vitamins, and microelements may affect the course of MS.

Views: The review presents data from studies published between 2017 and 2022.

Conclusions: There are numerous studies on the role of specific dietary components in the treatment of MS, but the results are still limited. More work is needed to define the tools required for the assessment of patients' eating habits because dietary factors can affect the functioning and quality of life of MS patients and should therefore be evaluated to assist in comprehensive treatment and recovery.

Key words: multiple sclerosis, nutrition, vitamins, macronutrients.

INTRODUCTION

Multiple sclerosis (MS) is a chronic demyelinating disease of the central nervous system with multifocal damage to the brain and spinal cord [1]. The current estimated prevalence of MS worldwide is 2.8 million people (35.9 per 100,000 inhabitants) [2]. The disease mainly affects young people, aged 20-40 years, with the average age of diagnosis being 32 [2, 3]. In 3-5% of all cases MS occurs before age 16 (early onset) and in 3.4-12.7% after 50 (late onset) [3]. MS affects twice as many women as men and is a common cause of disability in young adults [2]. The etiology of MS remains unclear but is often recognized by researchers as a multifactorial disease that involves an autoimmune and genetic predisposition combined with environmental influences (e.g., low vitamin D levels, smoking, obesity) [4, 5]. The disease can affect any region of the central nervous system (CNS) and generate almost any neurological symptom. The most common are sensory disturbances (numbness, tingling), balance and gait problems (as a result of weakness, fatigue), vision problems (double, blurred vision), digestive and urinary system dysfunctions, cognitive and emotional disorders [6]. Furthermore, MS is characterized by a wide range of symptoms that may be related to nutritional status and contribute to an increased risk of malnutrition. Diet-related health problems that are, however, often observed in the affected population, including cardiovascular disease and metabolic syndrome, which can contribute to deteriorated condition of the patient [7]. According to the current McDonald's MS criteria, modified in 2017, the presence of a long-term multifocal and neurological deficit, usually supported by magnetic resonance imaging and/or cerebrospinal fluid tests is the basis for confirming the diagnosis of MS [8]. MS is divided into four subtypes: relapsing-remitting multiple sclerosis (RRMS), primary progressive multiple sclerosis (PPMS), secondary progressive multiple sclerosis (SPMS), and clinically isolated syndrome (CIS). To confirm the diagnosis, other CNS diseases that may mimic MS should be excluded. The greatest challenge for scientists studying MS is the development of treatments that incorporate neuroprotection and remyelination to treat and ultimately prevent progressive forms of the disease [9]. Currently, there are

drugs available that modify the course of MS by reducing relapsing activity and slowing the progression of disability. Treatment should be personalized for each patient, depending on clinical status, disease activity, patient safety during long-term therapy with a particular drug, control of its use, and patient's preference [10]. Treatment of MS includes the support of physical therapists, occupational therapists, and nutritionists. Scientific evidence suggests that dietary factors can exacerbate or alleviate MS symptoms through various mechanisms (metabolic, inflammatory, etc.) in both primary progressive MS (PPMS) and relapsing-remitting MS (RRMS) [11, 12]. Nutritional therapy in multiple sclerosis should be based primarily on the individual condition of the patient, the level of nutrition of the patient's organism, as well as the stage of the disease and its current phase (relapse/remission). Therefore, the objective of the study was to check whether and, if so, to what extent, the intake of macronutrients, vitamins, and micronutrients may affect the course of MS.

METHODOLOGY

Due to the desire to comprehensively review current scientific research and to exhaust the topic, scientific studies presenting the relationship of nutrition and its components in patients with multiple sclerosis were analyzed. An online search was conducted using the following databases: PubMed, Google Scholar, Researchgate, Science Direct. Keywords used in the search include: "multiple sclerosis", "nutrition in MS", "diet in MS", "vitamins in MS", "sodium in MS", "alpha-lipoic acid in MS". The review presents data from the studies published between 2017 and 2022. Several articles published prior to 2017 were included to clarify the relationship between the dietary components and MS.

MACRONUTRIENTS IN THE DIET OF MS PATIENTS

Current scientific research shows that in patients with multiple sclerosis, at the time of the onset of the disease, there is a wide spread of unhealthy eating habits, which in the long term can be associated with a higher risk of concomitant metabolic and cardiovascular diseases [7]. The macro- and micronutrients in the diet can be substrates for the microbiota, which in recent years has become a specific subject of research in MS [13-16].

PROTEINS

A recently published case-control study in a southern European cohort showed that patients with the first demyelinating episode admitted to lower plant protein intake and higher animal protein intake compared to healthy controls [17]. The role of animal proteins in the risk of developing multiple sclerosis is controversial. In 2016, a link was suggested between increased meat consumption and higher risk of multiple sclerosis [18]. Scientific reports of 2019 from Australia suggested a possible protective role of the consumption of unprocessed red meat on the risk of central nervous system demyelination in women [19]. Fitzgerald *et al.*, in a study evaluating the quality of the diet of MS patients, showed that a diet with lower red meat consumption was associated with a lower level of disability [20]. However, it is not known whether eating unprocessed red meat is associated with disease progression in people diagnosed with MS.

MS's physiological and/or immunological characteristics reduce metabolism of serotonin which is a neurotransmitter associated with affective and cognitive functions. Although the exact role of serotonin in MS is unclear, there are clear indications that axonal degeneration, pro-inflammatory cytokines, and MS-related changes affect the metabolic pathway of tryptophan (TRP; a serotonin precursor) leading to serotonergic deregulation and consequent dysfunctions such as anxiety, depressed mood, problems with attention and memory. In a double-blind, placebo-controlled study by Lieben *et al.*, MS patients with (n = 15) and without (n = 17) depressed mood took a whey protein mix with 4 different amounts of tryptophan. The addition of tryptophan with a mixture of whey proteins to the diet of MS patients was shown to improve memory processes, but did not improve mood [21]. The pilot study investigated two clinical

Table 1. Eligibility criteria

Inclusion criteria	Exclusion criteria
Articles in English Publication date between 2017 and July 2022 Meta-analysis Systematic reviews Randomized controlled clinical trials Cohort studies Prospective studies Pilot studies Cross-sectional studies Clinical-control studies Animal studies	Articles in a language other than English Publications on the use of a specific diet, e.g. ketogenic, Swank, Wahlsa, Mediterranean *In vitro* and *in vivo* studies Case reports

groups of patients with relapsing-remitting MS who had been following a high-vegetable/low-protein diet ($n = 10$) and a Western diet (WD) ($n = 10$) for at least 12 months. Compared to WD, the study group showed a decrease in pro-inflammatory IL-17+ and PD-1+ T cells and an increase in anti-inflammatory PD-L1+ monocytes; however, the described effects were mainly attributed to diet-related changes in the microbiota of MS patients and not to the amount of protein in the diet [22].

Furthermore, in an animal model study, it was shown that reducing protein intake, and in particular restricting amino acid tryptophan intake, prevents the induction of EAE (experimental autoimmune encephalomyelitis) induction by inhibiting T cell responses [23]. This effect depends on the diversity of the microbiota, as the reduction of tryptophan in the diet leads to enrichment of the types of bacteria that synthesize tryptophan.

FATS

In the 1950s, Swank *et al.* observed that people who consumed less animal fat than the typical "Western Diet" had a lower incidence of MS [24]. Obesity (attributed to excessive consumption of dietary fat) has also been shown to have a negative impact on the disease, especially if it occurs in adolescence [25]. According to existing scientific evidence, serum lipid levels and body mass index (BMI) are significantly related to the level of disability and its progression in people with MS [26]. A characteristic feature of a typical Western diet is increased fat consumption, especially saturated fatty acids (SFA), ω-6 polyunsaturated fatty acids, and trans fats, accompanied by a general reduction in ω-3 consumption, which also contributes to the changes in the values of the lipid profile. A pilot study by Albrechtsen *et al.* showed that fat consumption (33.9 ± 5.5% of total energy consumption) in the diet of MS patients was inversely related to physical performance (i.e. 6MWT – 6-minute walk test and VO_{2max}) [27]. Bromley *et al.*, in a cross-sectional study, showed significant correlations between the percentage of fat intake from patients with improved distance traveled in 6MWT ($r = 0.51$, $p = 0.02$) and the results of the short-form health survey of 36 items (SF-36) ($r = 0.47$, $p = 0.03$), which means that diets with a higher fat content were positively correlated with improved mobility and quality of life in people with mild to moderate MS [28].

Saturated fatty acids

Current research is paying particular attention to the type of fat consumed in the diet. The fatty acids that are most often described in the literature as harmful for MS are saturated fatty acids (SFA). It is generally accepted that saturated fat consumption increases LDL cholesterol, which is associated with poor MS outcomes [29-31]. Saturated fat can also directly affect the immune system by activating pro-inflammatory receptors, leading to additional consequences, including increased NF-κB [32]. The key role of abnormal activation of NF-κB is in the activation of pro-inflammatory activity in the pathogenesis of MS. The therapeutic efficacy of many approved MS treatments is currently believed to be attributed, at least in part, to blockade of the NF-κB pathway of the peripheral nervous system and the immune response of the CNS [33]. In a prospective study, it was found that in children with multiple sclerosis, high fat energy consumption, especially an excessive supply of saturated fat, can increase the risk of disease recurrence [34]. In the study mentioned above by Bromley *et al.* the percentage of saturated fat consumed in the diet by MS patients was shown to be correlated with vitality, which measures overall fatigue/energy ($r = –0.45$, $p = 0.04$) [26].

Polyunsaturated fatty acids

The alleged role of low polyunsaturated fatty acids (PUFA) intake as a risk factor for MS is still being discussed. PUFA can have anti-inflammatory and immunomodulatory effects, reducing inflammation by converting to anti-inflammatory prostaglandins E_1 and E_2, with further effects on cytokine production, leukocyte migration, and other components of the immune system [35]. These include omega-6 fatty acids (e.g. linoleic acid) and omega-3 fatty acids (e.g. α-linolenic acid [ALA], eicosapentaenoic acid [EPA], and docosahexaenoic acid [DHA]). It should be noted that the studies conducted so far in MS have been largely related to supplementation with PUFA and not its consumption in the diet.

The effectiveness of the supplementation dose varies depending on many factors, especially the progression and state of the disease before starting supplementation. More research is needed to determine the effectiveness of omega-3 fatty acids in the health of MS patients [41]. The lack of standardized implementation continues to be a major problem in existing clinical trials, including discrepancies in doses, sources, small group sizes, and varying duration of treatment.

Alpha-lipoic acid

Recently, researchers have paid special attention to the efficacy of lipoic acid (LA) therapy in diseases of the central nervous system [42]. Supplementation is a promising approach to improve the outcomes of MS patients. Lipoic acid protects the central nervous system through immunomodulation and antioxidants, prevents inflammatory cells from crossing the blood-brain barrier (BBB) and protects brain endothelial cells. In the CNS, LA inhibits the activity of T cells/microglia, reduces the expression of TNF-α and IFN-γ, and neutralizes ROS and NO [43]. LA may be able to attenuate lesion activity

Table 2. Analysis of polyunsaturated fatty acids (PUFA) consumption and supplementation in multiple sclerosis patients in research studies

Authors	Type of study	Year	Supplementation/ Dietary intake	Results	Conclusions
Zandi-Esfahan *et al.* (36)	Randomized controlled trial (50 patients with RRMS aged 18-45)	2017	Supplementation 1 g/day of fish oil	No differences were found between serum TNF-α, IFN-γ, IL-6 and IL-1β levels at the three time points between the two groups ($p > 0.05$). There were no statistically significant differences in mean EDSS between the experimental and control groups after 12 months of intervention ($p = 0.08$).	Administration of fish oil did not reduce serum TNF-α, IL1β, IL-6 and IFN-γ compared to placebo. There was no evidence of an effect on the degree of disability in the patients.
Bjørnevik *et al.* (37)	Prospective study – 80,920 women of the Nurses' Health Study (1984-2004) and 94,511 women of the Nurses' Health Study II (1991-2009) who reported on diet every 4 years and identified 479 incident MS cases during follow-up	2017	Dietary intake	Increased consumption of PUFA was associated with a reduced risk of MS. Only plant-derived ALA was significantly associated with a lower risk of MS. The researchers did not find a significant association between the intake of marine n-3 fatty acids and the risk of MS.	A significant inverse association between PUFA intake and MS risk. The effects estimates were only significant for plant-derived n-3 ALA, and not for marine n-3 fatty acids. Low PUFA intake may be another modifiable risk factor for MS.
Sedighiyan *et al.* (38)	A systematic review and meta-analysis	2019	Supplementation	Omega-3 supplementation did not have a significant effect on the disability status scale (EDSS) of the patients, as well as on the serum levels of serum IL-1β and IL-6. However, they significantly decreased the concentration of TNF-α compared to placebo.	According to researchers, omega-3 supplementation may not have a clinically significant effect on EDSS or pro-inflammatory markers.
Langer-Gould *et al.* (39)	Clinical trial	2020	Dietary intake	Eating fish/seafood at least once a week or at least once a month with regular use of fish oil was associated with a 44% reduction in the probability of developing MS/CIS (OR = 0.56; 95% CI = 0.41-0,76; $p = 0.0002$) compared to the consumption of fish/seafood less than once a month and without supplementation with fish oil.	Various genes and proteins related to fatty acid metabolism have been shown to be associated with the incidence and prognosis of MS. The intake of omega-3 fatty acids may be an important modifiable risk factor for MS.
Aristotelous *et al.* (40)	Randomized controlled trial (51 patients with RRMS and low disability scores, age: 38.4 ± 7.1 years, treated with interferon-β)	2021	24-month supplementation with a cocktail of dietary supplement formula, NeuroaspisTM PLP10, containing specific omega-3 and omega-6 PUFA and specific antioxidant vitamins: A, E, γ-tocopherol	The dietary supplement significantly improved the single support time and the stride time ($p < 0.05$), both of the gait time-space parameters. GDI in the placebo group decreased by approximately 10% after 24 months and increased by approximately 4% in the test group ($p < 0.05$).	Long-term supplementation with high doses of omega-3 and omega-6 PUFAs and specific antioxidant vitamins improved some functional capacity and gait parameters in patients with RRMS.
AlAmmar *et al.* (41)	A systematic review	2021	Supplementation	Benefits of supplementing with 4 g of fish oil or omega-3 daily in MS patients.	Supplementation can affect the level of inflammatory markers such as TNF-α, IL-Iβ, IFN-γ and IL-6, the quality of life of patients, and the progression of MS. The effectiveness of the dose varies depending on many factors, especially the progression and state of the disease before starting supplementation.

by modulating monocyte and macrophage inflammation and phagocytosis, and cAMP (cyclic adenosine-3', 5'-monophosphate) may mediate these effects [44]. Demyelination, oxidative stress, and autoimmunity are typical features of MS, so the use of LA as a dietary supplement or combination therapy is a promising and safe strategy in the future. The achievements of LA supplementation to date are exciting, but the evidence is heavily limited primarily by the short duration of the trial and insufficient research. Researchers also consider its supplementation in terms of low bioavailability after oral administration, which is a key factor preventing its use [45]. Cameron *et al.* compared gastrointestinal tolerance and assessed R-lipoic acid (LA) absorption in subjects with progressive multiple sclerosis in a single-center, randomized, double-blind, crossover study. Participants took 600 mg of R-LA or 1,200 mg of a 1 : 1 racemic mixture of R, S-LA in single daily doses for 7 to 10 days [46]. People with PPMS had better gastrointestinal tolerance and serum absorption of R-LA when 600 mg of R-LA was taken as R-LA alone than when it was taken as a racemic R, S-LA mixture.

CARBOHYDRATES

In patients with the first episode of demyelinating, a higher consumption of simple carbohydrates and a lower consumption of insoluble fiber were observed [17]. Fitzgerald *et al.* in a study evaluating the quality of the diet of MS patients showed that a diet richer in fiber, that is, fruits, vegetables, legumes and whole grains, and poorer in simple sugars (sugar-sweetened sweets and drinks) was associated with a lower level of disability [20]. In a pilot study, Albrechtsen *et al.* showed that carbohydrate consumption (46.4 ± 7.1% of total energy intake) was positively associated with physical performance in patients with MS (i.e. 6MWT and VO_{2max}), while high sugar consumption was associated with elevated serum insulin levels, which can lead to inflammation and worsening of MS [25]. Bromley *et al.* showed significant correlations between the consumption of carbohydrates by MS patients, which was associated with the reduction in the distance traveled during 6MWT and the self-assessment of walking ability and less physical activity, while diets high in simple sugars were associated with slower timed 25 foot walk, G – T25FW test results ($r = 0.43$, $p = 0.05$) and reduced physical – activity ($r = –0.51$, $p = 0.05$). This means that diets with a lower carbohydrate content were positively correlated with improved mobility, physical activity, and quality of life in people with mild to moderate MS [28].

In one of the pilot studies on vitamin B_1 consumption in patients with multiple sclerosis, patients who consumed fewer total carbohydrates and mainly simple carbohydrates showed a higher level of depression, which is characteristic of MS [47]. A lower total carbohydrate intake than recommended can interfere with vitamin B_1 activity because its function is to metabolize carbohydrates to obtain glucose as a source of neuronal energy [48]. In a multicenter study of the pediatric population, no association was found between the consumption of protein, fat, carbohydrates, fiber, fruit, vegetables or dairy products between the MS group and the control group [49].

The high consumption of simple carbohydrates has been suggested to be generally pro-inflammatory [50], but its role in MS requires further research. High dietary fiber intake can modulate the intestinal microbiota and the end products of fiber fermentation, short-chain fatty acids (SCFA), can modify the immune microenvironment of the gut by inducing regulatory T lymphocytes and protect against autoimmune diseases [17]. However, in relation to MS, there are insufficient research results.

VITAMINS

Vitamin D

Vitamin D is a fat-soluble vitamin characterized best by its role in calcium homeostasis, which can be taken in the diet or synthesized during exposure to the sun. It is also the most promising vitamin for the treatment of chronic autoimmune and inflammatory diseases. Vitamin D deficiency is a risk factor for the development of MS, as well as a negative prognostic factor in MS, it can modulate the activity and progression of the disease [51]. Evidence is emerging that vitamin D plays an important role in the pathogenesis of MS due to its regulatory effect on the immune system, particularly in the activation and proliferation of lymphocytes and the differentiation of helper T lymphocytes [52, 53]. An 11-year follow-up of patients has shown that adequate vitamin D levels can contribute to long-term neuroprotection in people with multiple sclerosis. These results suggest that vitamin D supplementation and abandonment of smoking early after MS diagnosis may protect long-term cognitive function and central nervous system integrity in patients, regardless of disease-modifying therapy [54].

Observational studies suggest that circulating vitamin D levels are a sign of more active disease in patients with relapsing-remitting multiple sclerosis [55]. A meta-analysis of randomized controlled trials showed that vitamin D supplementation had no effect on the Expanded Disability Status Scale (EDSS) in MS patients [56], although contradictory results were found [57]. Some limitations were also shown, i.e., a small number of included studies and publication bias. Researchers have shown that vitamin D supplementation supports the treatment of MS patients and reduces the appearance of depression symptoms [58-61], although studies on this issue are contradictory and inconclusive [62]. Future research on vitamin D and MS depression symptoms should include patients with actual

depression symptoms at baseline and include confounders such as exposure to the sun.

Some studies show that vitamin D in moderate concentrations can exert a direct immunoregulatory effect, while supplementation at too high doses can mimic the exacerbation of MS symptoms, causing fatigue, urinary tract disorders and weakness, and even leading to life-threatening complications [63]. The study by Feige *et al.*, presented data from clinical trials in which vitamin D doses ranged from 10,000 to 40,000 IU/day, which appeared to be safe as supplement therapy. The side effects in the studies were usually minor and manageable. However, current data are insufficient and larger randomized controlled trials are required to determine the effect of high-dose vitamin D supplementation on multiple sclerosis. Given these limitations, vitamin D supplementation in MS is an issue that should be monitored by doctors.

Vitamin B_{12} and folic acid

Vitamin B_{12} (cobalamin) plays a fundamental role in the functioning of the central nervous system, especially in the conversion of homocysteine to methionine through methionine synthase, which is essential for DNA and RNA synthesis. Cobalamin deficiency can lead to elevated levels of homocysteine. Vitamin B_{12} plays an important role in multiple sclerosis due to its participation in the formation of the myelin sheath and its immunomodulatory and neurotrophic effects [64]. A meta-analysis of scientific studies by Dardiotis *et al.*, did not show significant differences in vitamin B_{12} levels between people with multiple sclerosis and controls, although the blood of people with multiple sclerosis showed higher levels of homocysteine [65]. Similar conclusions were obtained in a recently published meta-analysis, which also found higher levels of homocysteine in the serum of MS patients compared to the control group [66]. Elevated levels of homocysteine play a role in myelin sheath degeneration by disrupting methyl group donors, causing neuritis, microglial activation, and other biochemical reactions in the central nervous system [67]. A recent double-blind clinical study was conducted to determine the effects of vitamin B_{12} and folate supplementation on serum homocysteine in patients with RRSM. In the 'vitamin group', the mean homocysteine level was shown to be significantly reduced and the physical and mental areas of quality of life improved [68]. Supplementation with vitamin B_{12} and folate can lower serum homocysteine level in MS, which would be helpful in possible MS treatment strategies in clinical practice.

Other B vitamins

Vitamin B_1

Deficiency or lack of thiamine activity (vitamin B_1) causes neurological symptoms, especially symptoms of depression, inherent in multiple sclerosis and related to its pathogenesis. In a pilot study by Orti *et al.*, a significant negative correlation was found between depression and thiamine consumption [47]. The dietary intake associated with thiamine activity in the MS patient population exhibits an imbalance characterized by a lower recommended total carbohydrate intake, which consists mainly of simple carbohydrates. These results demonstrated the importance of determining the intake of vitamin B_1 and its main nutritional sources in MS patients with severe depression.

Vitamin B_7

Biotin (vitamin B_7, H), as a cofactor of the four essential carboxylases, can support myelin repair by increasing fatty acid synthesis and protect against hypoxia-induced axonal degeneration by increasing energy production in neurons. Some researchers have focused on administering high-dose biotin (HDB) to MS patients. Clinical data show that patients with multiple sclerosis, when treated with daily doses of biotin of up to 300 mg, responded positively, reversing disease progression and reducing chronic disability [69]. The likely mechanism is due to increased myelin production that leads to increased axonal remyelination. Biotin may also increase energy production and reduce axonal hypoxia in multiple sclerosis [69, 70]. In current publications, it turns out that it may cause relapses and increase its activity. The mechanism by which HDB can increase the activity of MS disease is unclear. It has been hypothesized to compete with the metabolism or transport of B vitamins, including riboflavin, which are involved in cell function [71]. However, the results are still inconclusive [72]. Motte *et al.* concluded in their study that a high oral dose of biotin cannot be recommended for patients with progressive multiple sclerosis and that further research on biotin is no longer needed [73].

Vitamin B_2

Vitamin B_2 (riboflavin), in addition to a number of important functions it performs in the human body (important for the proper functioning of the nervous, endocrine, cardiovascular, and immune systems), plays an important role in myelin formation. A recent scientific review of its role in MS concluded that riboflavin may be considered a likely complementary agent to reduce the harmful effects of neurological disability in multiple sclerosis; however, most research in this area is limited to experimental studies, so more interventional studies are needed in human populations to determine the effect of riboflavin [74].

Table 3. Discussion of key nutritional strategies in patients with multiple sclerosis

	Recommended nutritional strategies	Unrecommended nutritional strategies
Macronutrients	Dietary intake of plant protein, foods rich in complex carbohydrates and fiber. Ensuring an adequate quantity and quality of dietary fats (adequate supply of omega-3 fatty acids).	Excessive intake of macronutrients, especially simple carbohydrates, trans fatty acids, saturated fatty acids.
Vitamin D	Ensure adequate supplementation with plasma vitamin D levels under medical supervision.	Supplementation in excessively high doses without medical consultation.
Vitamin B_1 (thiamine)	An adequate dietary supply of vitamin B is recommended, due to the results of studies that have shown a correlation between the lower recommended total carbohydrate intake as the main sources of vitamin B_1 and the appearance of depression in patients with MS.	
Vitamin B_2 (riboflavin)	Due to its role in myelin formation, an adequate supply in the diet is worth keeping in mind. Further research is needed to determine its potential impact on multiple sclerosis.	
Vitamin B_7 (biotin)	According to current research, oral high-dose biotin cannot be recommended for patients with progressive multiple sclerosis.	
Vitamin B_{12} and folic acid	Deficiency of these vitamins can lead to increased levels of homocysteine. Supplementation with vitamin B_{12} and folic acid can lower serum homocysteine levels in MS, which would be helpful for possible MS treatment strategies in clinical practice. More research is needed.	
Sodium	According to current research, dietary salt intake does not affect the course and activity of MS. However, more research is needed due to sodium storage in MS patients to determine whether this is a cause or effect of the disease.	

MINERALS

Sodium

Preclinical studies before the analyzed period suggested the possible adverse effects of a high-salt diet in multiple sclerosis. Salt (NaCl, sodium chloride) has been suggested to potentially influence MS activity and progression, possibly by modulating T-cell differentiation [75]. In a randomized clinical trial by Fitzgerald *et al.*, over a 5-year follow-up of 468 patients, it was investigated whether a salt-rich diet, measured by urine sodium concentration, was associated with faster disease progression, as well as activity and disability [76]. Dietary salt intake has not been shown to have an effect on the course and activity of MS. Cortese *et al.*, obtained similar results, showing no correlation between sodium intake and the risk of MS [77]. Although some researchers question the assumption that increased sodium intake is directly correlated with sodium excretion [78]. Epidemiological data also do not confirm the strong influence of high sodium intake on the appearance of MS. The Asian population is exposed to a salty diet, but the prevalence of MS in Asian countries is among the lowest in the world [79, 80]. Researchers are still searching for an answer to this relationship and show that sodium accumulates in large amounts in muscle and interstitial tissue, creating an electrolyte environment that does not balance with plasma and, therefore, escapes the control of the kidneys. The storage of sodium in the skin has been shown to be based on non-renal regulatory mechanisms that involve the immune system [81]. An observational study by Huhn *et al.*, provided data that increased the importance of skin as sodium storage and concluded that these results may further present skin for future research on salt as a pro-inflammatory agent driving autoimmune neuritis, such as in multiple sclerosis [82]. According to researchers, longitudinal studies are necessary to determine whether an increase in sodium content in the skin precedes the development of MS or is a consequence of the disease [83, 84].

Based on the scientific work published to date, Table 3 summarizes the dietary strategies described in MS patients.

CONCLUSIONS

Research on the role of individual nutritional components in multiple sclerosis is progressing, but remains limited today. These studies are of variable quality, often with small sample sizes and a pilot cross-sectional design, and while some are good quality RCTs, their observation period is too short and the samples too small to draw definitive and reliable conclusions. More work is needed to define the tools to assess eating habits in MS patients because dietary factors can affect the functioning and quality of life of MS patients and should therefore be evaluated to assist in comprehensive treatment and recovery.

Conflict of interest

Absent.

Financial support

Absent.

References

1. Lassmann H. Multiple sclerosis pathology. Cold Spring Harb Perspect Med 2018; 8: a028936.
2. Walton C, King R, Rechtman L, Kaye W, Leray E, Marrie RA, et al. Rising prevalence of multiple sclerosis worldwide: insights from the Atlas of MS, third edition. Mult Scler 2020; 26: 1816-1821.
3. Alroughani R, Akhtar S, Ahmed S, Behbehani R, Al-Hashel J. Is time to reach EDSS 6.0 faster in patients with late-onset versus young-onset multiple sclerosis? PLoS One 2016; 11: e0165846.
4. Ghasemi N, Razavi S, Nikzad E. Multiple sclerosis: pathogenesis, symptoms, diagnoses and cell-based therapy. Cell J 2017; 19: 1-10.
5. Larsson SC, Burgess S. Causal role of high body mass index in multiple chronic diseases: a systematic review and meta-analysis of Mendelian randomization studies. BMC Med 2021; 19: 320.
6. Gelfand JM. Multiple sclerosis: diagnosis, differential diagnosis, and clinical presentation. Handb Clin Neurol 2014; 122: 269-290.
7. Esposito S, Bonavita S, Sparaco M, Gallo A, Tedeschi G. The role of diet in multiple sclerosis: a review. Nutr Neurosci 2018; 21: 377-390.
8. Thompson AJ, Banwell BL, Barkhof F, Carroll WM, Coetzee T, Comi G, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol 2018; 17: 162-173.
9. Thompson AJ, Baranzini SE, Geurts J, Hemmer B, Ciccarelli O. Multiple sclerosis. Lancet 2018; 391: 1622-1636.
10. Torkildsen Ø, Myhr KM, Bø L. Disease-modifying treatments for multiple sclerosis – a review of approved medications. Eur J Neurol 2016; 23: 18-27.
11. Altowaijri G, Fryman A, Yadav V. Dietary interventions and multiple sclerosis. Curr Neurol Neurosci Rep 2017; 17: 28.
12. Riccio P, Rossano R. Nutrition facts in multiple sclerosis. ASN Neuro 2015; 7: 1759091414568185.
13. Sanders DJ, Inniss S, Sebepos-Rogers G, Rahman FZ, Smith AM. The role of the microbiome in gastrointestinal inflammation. Biosci Rep 2021; 41: BSR20203850.
14. Sanchez JMS, DePaula-Silva AB, Libbey JE, Fujinami RS. Role of diet in regulating the gut microbiota and multiple sclerosis. Clin Immunol 2022; 235: 108379.
15. Engelenburg HJ, Lucassen PJ, Sarafian JT, Parker W, Laman JD. Multiple sclerosis and the microbiota: progress in understanding the contribution of the gut microbiome to disease. Evol Med Public Health 2022; 10: 277-294.
16. Wang X, Liang Z, Wang S, Ma D, Zhu M, Feng J. Role of gut microbiota in multiple sclerosis and potential therapeutic implications. Curr Neuropharmacol 2022; 20: 1413-1426.
17. Cavalla P, Golzio P, Maietta D, Bosa C, Pasanisi MB, et al. Dietary habits, nutritional status and risk of a first demyelinating event: an incident case-control study in a southern European cohort. Neurol Sci 2022; 43: 4373-4380.
18. t'Hart BA. Why does multiple sclerosis only affect human primates? Mult Scler 2016; 22: 559-563.
19. Black LJ, Bowe GS, Pereira G, Lucas RM, Dear K, van der Mei I, Sherriff JL; Ausimmune Investigator Group. Higher non-processed red meat consumption is associated with a reduced risk of central nervous system demyelination. Front Neurol 2019; 10: 125.
20. Fitzgerald KC, Tyry T, Salter A, Cofield SS, Cutter G, Fox R, Marrie RA. Diet quality is associated with disability and symptom severity in multiple sclerosis. Neurology 2018; 90: e1-e11.
21. Lieben CK, Blokland A, Deutz NE, Jansen W, Han G, Hupperts RM. Intake of tryptophan-enriched whey protein acutely enhances recall of positive loaded words in patients with multiple sclerosis. Clin Nutr 2018; 37: 321-328.
22. Saresella M, Mendozzi L, Rossi V, Mazzali F, Piancone F, LaRosa F, et al. Immunological and clinical effect of diet modulation of the gut microbiome in multiple sclerosis patients: a pilot study. Front Immunol 2017; 8: 1391.
23. Sonner JK, Keil M, Falk-Paulsen M, Mishra N, Rehman A, Kramer M, et al. Dietary tryptophan links encephalogenicity of autoreactive T cells with gut microbial ecology. Nat Commun 2019; 10: 4877.
24. Swank RL, Lerstad O, Strøm A. Multiple sclerosis in rural Norway its geographic and occupational incidence in relation to nutrition. N Engl J Med 1952; 246: 722-728.
25. Munger KL. Childhood obesity is a risk factor for multiple sclerosis. Mult Scler 2013; 19: 1800.
26. Zhang Y, Zhou Y, van der Mei IAF, Simpson S, Ponsonby AL, Lucas RM, et al.; Ausimmune/AusLong Investigators Group. Lipid-related genetic polymorphisms significantly modulate the association between lipids and disability progression in multiple sclerosis. J Neurol Neurosurg Psychiatry 2019; 90: 636-641.
27. Albrechtsen MT, Langeskov-Christensen M, Jørgensen MLK, Dalgas U, Hansen M. Is diet associated with physical capacity and fatigue in persons with multiple sclerosis? – Results from a pilot study. Mult Scler Rel Dis 2020; 40: 101921.
28. Bromley L, Horvath PJ, Bennett SE, Weinstock-Guttman B, Ray AD. Impact of nutritional intake on function in people with mild-to-moderate multiple sclerosis. Int J MS Care 2019; 21: 1-9.

29. Tettey P, Simpson S, Taylor B, Ponsonby AL, Lucas RM, Dwyer T, et al. An adverse lipid profile and increased levels of adiposity significantly predict clinical course after a first demyelinating event. J Neurol Neurosurg Psychiatry 2017; 88: 395-401.
30. Uher T, Fellows K, Horakova D, Zivadinov R, Vaneckova M, Sobisek L, et al. Serum lipid profile changes predict neurodegeneration in interferon-beta1a-treated multiple sclerosis patients. J Lipid Res 2017; 58: 403-411.
31. Haase S, Haghikia A, Gold R, Linker RA. Dietary fatty acids and susceptibility to multiple sclerosis. Mult Scler 2018; 24: 12-16.
32. Katz Sand I. The role of diet in multiple sclerosis: mechanistic connections and current evidence. Curr Nutr Rep 2018; 7: 150-160.
33. Zhou Y, Cui C, Ma X, Luo W, Zheng SG, Qiu W. Nuclear factor κB (NF-κB)-mediated inflammation in multiple sclerosis. Front Immunol 2020; 11: 391.
34. Azary S, Schreiner T, Graves J, Waldman A, Belman A, Weinstock Guttman B, et al. Contribution of dietary intake to relapse rate in early paediatric multiple sclerosis. J Neurol Neurosurg Psychiatry 2018; 89: 28-33.
35. von Geldern G, Mowry EM. The influence of nutritional factors on the prognosis of multiple sclerosis. Nat Rev Neurol 2012; 8: 678-689.
36. Zandi-Esfahan S, Fazeli M, Shaygannejad V, Hasheminia J, Badihian S, Aghayerashti M, Maghzi H. Evaluating the effect of adding fish oil to fingolimod on TNF-α, IL1β, IL6, and IFN-γ in patients with relapsing-remitting multiple sclerosis: a double-blind randomized placebo-controlled trial. Clin Neurol Neurosurg 2017; 163: 173-178.
37. Bjørnevik K, Chitnis T, Ascherio A, Munger KL. Polyunsaturated fatty acids and the risk of multiple sclerosis. Mult Scler 2017; 23: 1830-1838.
38. Sedighiyan M, Djafarian K, Dabiri S, Abdolahi M, Shab-Bidar S. The effects of omega-3 supplementation on the expanded disability status scale and inflammatory cytokines in multiple sclerosis patients: a systematic review and meta-analysis. CNS Neurol Disord Drug Targets 2019; 18: 523-529.
39. Langer-Gould A, Black LJ, Waubant E, Smith JB, Wu J, Gonzales EG, et al. Seafood, fatty acid biosynthesis genes, and multiple sclerosis susceptibility. Mult Scler 2020; 26: 1476-1485.
40. Aristotelous P, Stefanakis M, Pantzaris M, Pattichis CS, Calder PC, Patrikios IS, et al. The effects of specific omega-3 and omega-6 polyunsaturated fatty acids and antioxidant vitamins on gait and functional capacity parameters in patients with relapsing-remitting multiple sclerosis. Nutrients 2021; 13: 3661.
41. AlAmmar WA, Albeesh FH, Ibrahim LM, Algindan YY, Yamani LZ, Khattab RY. Effect of omega-3 fatty acids and fish oil supplementation on multiple sclerosis: a systematic review. Nutr Neurosci 2021; 24: 569-579.
42. Seifar F, Khalili M, Khaledyan H, Moghadam SA, Izadi A, Azimi A, Shakouri SK. α-Lipoic acid, functional fatty acid, as a novel therapeutic alternative for central nervous system diseases: a review. Nutr Neurosci 2019; 22: 306-316.
43. Xie H, Yang X, Cao Y, Long X, Shang H, Jia Z. Role of lipoic acid in multiple sclerosis. CNS Neurosci Ther 2022; 28: 319-331.
44. Fiedler SE, Spain RI, Kim E, Salinthone S. Lipoic acid modulates inflammatory responses of monocytes and monocyte-derived macrophages from healthy and relapsing-remitting multiple sclerosis patients. Immunol Cell Biol 2021; 99: 107-115.
45. Kong D, Saqer AA, Carpinelli de Jesus M, Khan N, Jones A, Blanchfield JT, et al. Design, synthesis and evaluation of alpha lipoic acid derivatives to treat multiple sclerosis-associated central neuropathic pain. Bioorg Med Chem 2022; 69: 116889.
46. Cameron M, Taylor C, Lapidus J, Ramsey K, Koop D, Spain R. Gastrointestinal tolerability and absorption of R- versus R,S-lipoic acid in progressive multiple sclerosis: a randomized crossover trial. J Clin Pharmacol 2020; 60: 1099-1106.
47. Ortí JER, Cuerda-Ballester M, Drehmer E, Carrera-Juliá S, Motos-Muñoz M, Cunha-Pérez C, et al. Vitamin B1 intake in multiple sclerosis patients and its impact on depression presence: a pilot study. Nutrients 2020; 12: 2655.
48. Ortigoza-Escobar JD, Alfadhel M, Molero-Luis M, Darin N, Spiegel R, de Coo IF, et al. Thiamine deficiency in childhood with attention to genetic causes: survival and outcome predictors. Ann Neurol 2017; 82: 317-330.
49. Pakpoor J, Seminatore B, Graves JS, Schreiner T, Waldman AT, Lotze TE, et al. US Network of Pediatric Multiple Sclerosis Centers. Dietary factors and pediatric multiple sclerosis: a case-control study. Mult Scler 2018; 24: 1067-1076.
50. Della Corte KW, Perrar I, Penczynski KJ, Schwingshackl L, Herder C, Buyken AE. Effect of dietary sugar intake on biomarkers of subclinical inflammation: a systematic review and meta-analysis of intervention studies. Nutrients 2018; 10: 606.
51. Munger KL, Levin LI, Hollis BW, Howard NS, Ascherio A. Serum 25-hydroxyvitamin D levels and risk of multiple sclerosis. JAMA 2006; 296: 2832-2838.
52. Dobson R, Giovannoni G. Multiple sclerosis – a review. Eur J Neurol 2019; 26: 27-40.
53. Khosravi-Largani M, Pourvali-Talatappeh P, Rousta AM, Karimi-Kivi M, Noroozi E, Mahjoob A, et al. A review on potential roles of vitamins in incidence, progression, and improvement of multiple sclerosis. ENeurologicalSci 2018; 10: 37-44.
54. Cortese M, Munger KL, Martínez-Lapiscina EH, Barro C, Edan G, Freedman MS, et al. Vitamin D, smoking, EBV, and long-term cognitive performance in MS: 11-year follow-up of BENEFIT. Neurology 2020; 94: e1950-e1960.
55. Wang C, Zeng Z, Wang B, Shougang G. Lower 25-hydroxyvitamin d is associated with higher relapse risk in patients with relapsing-remitting multiple sclerosis. J Nutr Health Aging 2018; 22: 38-43.

56. Doosti-Irani A, Tamtaji OR, Mansournia MA, Ghayour-Mobarhan M, Ferns G, Daneshvar Kakhaki R, et al. The effects of vitamin D supplementation on expanded disability status scale in people with multiple sclerosis: a critical, systematic review and meta-analysis of randomized controlled trials. Clin Neurol Neurosurg 2019; 187: 105564.
57. Bagur MJ, Murcia MA, Jiménez-Monreal AM, Tur JA, Bibiloni MM, Alonso GL, Martínez-Tomé M. Influence of diet in multiple sclerosis: a systematic review. Adv Nutr 2017; 8: 463-472.
58. Hongell K, Silva DG, Ritter S, Meier DP, Soilu-Hänninen M. Efficacy and safety outcomes in vitamin D supplement users in the fingolimod phase 3 trials. J Neurol 2018; 265: 348-355.
59. Concerto C, Rodolico A, Ciancio A, Messina C, Natale A, Mineo L, et al. Vitamin D and depressive symptoms in adults with multiple sclerosis: a scoping review. Int J Environ Res Public Health 2021; 19: 199.
60. Głąbska D, Kołota A, Lachowicz K, Skolmowska D, Stachoń M, Guzek D. Vitamin D supplementation and mental health in multiple sclerosis patients: a systematic review. Nutrients 2021; 13: 4207.
61. El-Salem K, Khalil H, Al-Sharman A, Al-Mistarehi AH, Yassin A, Alhayk KA, et al. Serum vitamin d inversely correlates with depression scores in people with multiple sclerosis. Mult Scler Relat Disord 2021; 48: 102732.
62. Rolf L, Muris AH, Bol Y, Damoiseaux J, Smolders J, Hupperts R. Vitamin D3 supplementation in multiple sclerosis: symptoms and biomarkers of depression. J Neurol Sci 2017; 378: 30-35.
63. Feige J, Moser T, Bieler L, Schwenker K, Hauer L, Sellner J. Vitamin D supplementation in multiple sclerosis: a critical analysis of potentials and threats. Nutrients 2020; 12: 783.
64. Miller A, Korem M, Almog R, Galboiz Y. Vitamin B12, demyelination, remyelination and repair in multiple sclerosis. J Neurol Sci 2005; 233: 93-97.
65. Dardiotis E, Arseniou S, Sokratous M, Tsouris Z, Siokas V, Mentis AA, et al. Vitamin B12, folate, and homocysteine levels and multiple sclerosis: a meta-analysis. Mult Scler Relat Disord 2017; 17: 190-197.
66. Li X, Yuan J, Han J, Hu W. Serum levels of homocysteine, vitamin B12 and folate in patients with multiple sclerosis: an updated meta-analysis. Int J Med Sci 2020; 17: 751-761.
67. Obeid R, McCaddon A, Herrmann W. The role of hyperhomocysteinemia and B-vitamin deficiency in neurological and psychiatric diseases. Clin Chem Lab Med 2007; 45: 1590-1606.
68. Nozari E, Ghavamzadeh S. The effect of vitamin B12 and folic acid supplementation on serum homocysteine, anemia status and quality of life of patients with multiple sclerosis. Clin Nutr Res 2019; 8: 36-45.
69. Agrawal S, Agrawal A, Said HM. Biotin deficiency enhances the inflammatory response of human dendritic cells. Am J Physiol Cell Physiol 2016; 311: C386-391.
70. Sedel F, Bernard D, Mock DM, Tourbah A. Targeting demyelination and virtual hypoxia with high-dose biotin as a treatment for progressive multiple sclerosis. Neuropharmacology 2016; 110(Pt B): 644-653.
71. Goldschmidt CH, Cohen JA. The rise and fall of high-dose biotin to treat progressive multiple sclerosis. Neurotherapeutics 2020; 17: 968-970.
72. Mathais S, Moisset X, Pereira B, Taithe F, Ciron J, Labauge P, et al. Relapses in patients treated with high-dose biotin for progressive multiple sclerosis. Neurotherapeutics 2021; 18: 378-386.
73. Motte J, Gold R. High-dose biotin in multiple sclerosis: the end of the road. Lancet Neurol 2020; 19: 965-966.
74. Naghashpour M, Jafarirad S, Amani R, Sarkaki A, Saedisomeolia A. Update on riboflavin and multiple sclerosis: a systematic review. Iran J Basic Med Sci 2017; 20: 958-966.
75. Kleinewietfeld M, Manzel A, Titze J, Kvakan H, Yosef N, Linker RA, et al. Sodium chloride drives autoimmune disease by the induction of pathogenic TH17 cells. Nature 2013; 496: 518-522.
76. Fitzgerald KC, Munger KL, Hartung HP, Freedman MS, Montalbán X, Edan G, et al.; BENEFIT Study Group. Sodium intake and multiple sclerosis activity and progression in BENEFIT. Ann Neurol 2017; 82: 20-29.
77. Cortese M, Yuan C, Chitnis T, Ascherio A, Munger KL. No association between dietary sodium intake and the risk of multiple sclerosis. Neurology 2017; 89: 1322-1329.
78. Titze J. Sodium balance is not just a renal affair. Curr Opin Nephrol Hypertens 2014; 23: 101-105.
79. Bach JF. The hygiene hypothesis in autoimmunity: the role of pathogens and commensals. Nat Rev Immunol 2018; 18: 105-120.
80. Toussirot E, Béreau M, Vauchy C, Saas P. Could sodium chloride be an environmental trigger for immune-mediated diseases? An overview of the experimental and clinical evidence. Front Physiol 2018; 9: 440.
81. Wiig H, Luft FC, Titze JM. The interstitium conducts extrarenal storage of sodium and represents a third compartment essential for extracellular volume and blood pressure homeostasis. Acta Physiol (Oxf) 2018; 222.
82. Huhn K, Linz P, Pemsel F, Michalke B, Seyferth S, Kopp C, et al. Skin sodium is increased in male patients with multiple sclerosis and related animal models. Proc Natl Acad Sci U S A 2021; 118: e2102549118.
83. Donadieu M, Le Fur Y, Maarouf A, Gherib S, Ridley B, Pini L, et al. Metabolic counterparts of sodium accumulation in multiple sclerosis: a whole brain 23Na-MRI and fast 1H-MRSI study. Mult Scler 2019; 25: 39-47.
84. https://www.nationalmssociety.org/Living-Well-With-MS/Diet-Exercise-Healthy-Behaviors/Diet-Nutrition [Accessed: 31.07.2022].