International Journal of Nutrition Sciences

Journal Home Page: ijns.sums.ac.ir

Review Article

Dietetic Plans within the Multiple Sclerosis Community: A Review

Golnoush Mehrabani[1], Saeedeh Aminian[2], Golshid Mehrabani[3], Mina Rabiee[4*]

1. Department of Physical Therapy, Faculty of Rehabilitation Medicine, University of Alberta, Edmonton, Alberta, Canada
2. Centre for Physical Activity and Nutrition, Centre for Child Health Research, Auckland University of Technology, New Zealand
3. School of Dental Medicine, Boston University Henry M. Goldman, Boston, MA, USA
4. Department of Molecular Biology, ShahreKord Branch, Islamic Azad University, ShahreKord, Iran

ARTICLE INFO

Keywords:
Multiple sclerosis
Diet
Protein
Vitamin
Mineral

**Corresponding author:*
Mina Rabiee,
Department of Molecular Biology,
ShahreKord Branch,
Islamic Azad University,
ShahreKord, Iran
Tel: +98-71-32341025
Email: mina.rabiee1368@gmail.com

Received: December 6, 2017
Revised: November 9, 2018
Accepted: November 20, 2018

ABSTRACT

Multiple sclerosis (MS) is an immune-mediated, neurodegenerative diseasecaused by a complex interactionbetween lifetime environmental exposures and genes. Dieteic interventions environmental may affect the disease activity. These modifications may happen in intake of fats, proteins, calories, vitamins, minerals, fibers, and intake of several other nutrients which have a key role in neural health. This review was undertakento investigatethe role of nutritional modifications in patients with MS.

Please cite this article as: Mehrabani G, Aminian S, Mehrabani G, Rabiee M. Dietetic Plans within the Multiple Sclerosis Community: A Review. Int J Nutr Sci 2019;4(1):14-22.

Introduction

Multiple Sclerosis (MS) is a chronic, inflammatory, and immune-mediated diseaseresults in neurodegenerative processes in the nervous system, and is characterized by inflammation and myelin loss leading to a significant disability and unemployment because of the disease progression (1). The pathogenesis is complex and multifactorial (2) that is believed to be due to complex interaction between genetic and environmental exposures, such asnutritionthat can damage thenerve fibers and the myelin sheath of the nervous system (3, 4) and alterations in gut microbiome composition to down regulate the inflammatory process (5). Various environmental factors such as viral infection, brain injury, physical inactivity, obesity, smoking, low vitamin D level, etc. where shown to affect MS development (6, 7).

The disease is typically presented with motor impairment, visual disturbances, or sensory problems, pain, fatigue and cognitive impairment (8). MS has two main types and usually develops in young adults and usually women are more likely to be influenced. The first type is the relapsing-remitting MS (85%) with inflammation and demyelination as the primary pathology and the second type is primary progressive MS (15%) with neurodegeneration–axonal degeneration as the primary pathology (9). The prevalence of disease is higher in developed countries (10); with the highest prevalence in Scotland, Norway, Hungary, Slovenia, Germany, USA, Canada, and Czech Republic (11),

but is extremely rare in Japan and is almost unknown in the Indian subcontinent (12, 13). Treatment measures includechanges in lifestyle factors such as diet quality,disease-modifying,physical and occupational therapies and management of the symptom and relapses (14-17).

Dietary intervention is a simple and relatively low risk method to potentially promote and improve clinical status, well-being and life expectancy of MS patients (4). A variety of specific diets including plant-based low-fat McDougall (18), low saturated fat Swank (19), Mediterranean (17), ketogenic (9), energy restriction/fasting (20) andmodified Paleolithic (Paleo) Wahls™ (21, 22) diets were tried for treatment of MS disease, however, supportive evidences for the benefit of any specific dietary regimen are absent and well-designed, randomized controlled trials seem necessary (23). As currently, no spportive evidences are available to suggest a specific diet for MS.The National MS Society (NMSS) (24) recommended MS patients to follow healthy eating guidelines for the general population such as the US Dietary Guidelines for Americans (DGA) (25) and those for cancer and heart disease prevention (26).

Nutrition and MS

Dietary habits were reported as a possible environmental factor influencing the risk and progression of MS. There are not enough evidences to recommend a specific diet for MS patients and the National MS Society (NMSS) (25) just recommended MS patients to follow healthy eating guidelines for the general population such as the US Dietary Guidelines for Americans (DGA) (24) and those for cancer and heart disease prevention (26, 27).

Fat intake and MS

First studies on the effect of dietary fat on MS risk dates back to 1950 in Norway (28). It was shown that during progression of neuroinflammatory and neurodegenerative diseases such as MS, the myelin around the axons with lipid composition is influenced, so the intake of fatty acids was suggested as a factor that can affect the progression of the disease. It seems that a correlation between the increase in circulating total cholesterol levels, LDL-cholesterol, oxidized LDL and apolipoprotein B with adverse outcomes of the disease may exist (29) that were documented by consumption of saturated fatty acids, mainly from animal fat products regarding the mortality of MS disease (30).

In this relation, the neuroprotective effect of polyunsaturated fatty acids was demonstrated and was shown that polyunsaturated fatty acids inhibited the production of IL-1, IL-2, and TNF affecting the progression of the disease (31, 32). Therefore, Roy Swank developed a low-saturated fat diet pattern and exhibited that increased consumption of fat especially from meat and dairy sources would be associated with a higher incidence of MS (33). He suggested consumption of 20-30 g of fat per day that was later revised to ≤20 g of saturated fat (33) and again to ≤15 g would not lead to adverse events (34). Swank also reported that 5 g of cod liver oil, 10-15 g vegetable or fish oil, with one egg, multivitamins, whole wheat bread and fish ≥3 times per week would have neuroprotective effects and inhibit the progression of MS disease (35). Later, he increased oil consumption to 40-50 g per day in a diet consisted of an additional 10 g of fat from other sources such as bread with beneficial outcomes for patients with MS disease (35). His findings were later presented in a book entitled "Multiple Sclerosis Diet" (36). He also found that in patients who were diagnosed with relapsing remitting MS and were treated with a low saturated fat diet, exacerbations would be less frequent and less severe (37).

Base on Dietary Guidelines for Americans, monounsaturated and polyunsaturated fat in amounts within an individual's energy needs were recommended for patients with MS disease (24) as they are good sources of essential fatty acids, energy and vitamin E for weight maintenance (24). Institute of Medicine reported a dietary reference intake as an Acceptable Macronutrient Distribution Range (AMDR) for the total fat intake that should cover 20-35% of the energy (38). Later, the European Society for Parenteral and Enteral Nutrition (ESPEN) guideline for clinical nutrition in neurology suggested foods to be lower in saturated and higher in polyunsaturated fat for prevention of MS disease. In this guideline, omega-3 supplements were not suggested for patients with MS to reduce the disease relapse (39). It was shown that saturated fats can increase the translocation of endotoxins into the blood stream and activate the innate immune system and inflammatory cytokines that can affect MS related symptoms (40).

It was demonstrated that adequate amounts of polyunsaturated fatty acids incorporated into the neuronal cell membranes can protect neurons from the cytotoxic action of TNF via enhancement of the number of insulin receptors, because insulin secretion can silence the neurotoxic signal of TNF (41). So a high intake of omega-3 polyunsaturated fatty acid, particularly from fish sources was shown to significantly decrease the risk of CNS demyelination (42, 43). Lipoic acid as a nutritional

supplement can play an important role in normal mitochondrial function and stabilizing the integrity of the blood-brain barrier (BBB) in animal model of experimental autoimmune encephalomyelitis (EAE) due to its antioxidant, anti-inflammatory and immunomodulatory properties (44, 45). In mild inactive MS patients, a significant decrease in eicosapentaenoic acid (EPA), and a rise in dihomo-gammalinolenic and stearidonic acids in red blood cells were noted without any detectable EPA in adipose tissue and docosahexaenoic acid (DHA) in red blood cells and adipose tissue and reduction in linoleic acid (46).

In inflammatory, autoimmune and neurodegenerative disorders such as MS, polyunsaturated fatty acids, especially omega-3 fatty acids can have beneficial effects (47, 48). In these patients, fish oil can reduce the nitric oxide and cytokine levels due to its anti-inflammatory and neuroprotective properties (49). Fish oil supplemented with vitamins in newly diagnosed MS patients was demonstrated with conflicting results either improving the clinical outcome of the disease (50) or without any significant difference (51). These discrepancies may be due to variation in criteria applied for patient selection (clinical subtype of MS), and in disability scores at the start of the study (52).

In relapsing remitting MS, consumption of unsaturated fatty acids in hemp seed and evening primrose oils for 6 months was shown to significantly improve the score of Expanded Disability Status Scale (EDSS) (53). Identical findings were also reported in MS patients supplemented with eicosapentaenoic acid and DHA provided from fish oil (51). The obtained results may be due to immunomodulatory effects of n-3 polyunsaturated fatty acids e.g. in (Mediterranean diet) and the significant decrease in proinflammatory cytokines such as IL-1β, IL-2 and TNF-α and proinflammatory eicosanoids such as leukotriene B4 and prostaglandin E2 in MS subjects (52, 54).

The anti-inflammatory property of cod liver oil was demonstrated before leading to a lower risk of developing MS because cod liver oil is a rich source of vitamin A and D, EPA and DHA (33, 55, 56). Swank estimated consumption of DGA HEP oil for 1600-3200 kcal diets to lower the risk of disease in MS patients (57). He suggested the intake of saturated fat to be ≤15 g per day from meat and dairy sources and mono and polyunsaturated fats in amounts of 20-50 g per day based on energy needs by consuming olive, safflower, sunflower, soybean, sesame, canola, flaxseed, cottonseed, linseed, and peanut oils in the diet to reduce the risk of disease in MS patients (58).

High Fiber Diets and MS

The health benefits of high fiber diets in reduction of the risk of obesity, type 2 diabetes, colon

cancer, stroke, and cardiovascular diseases have led to the widely recommendation of high fiber diets. It was shown that high fiber diets can increase the blood levels of circulating butyrate as a multi-functional molecule affecting directly on the CNS function. Butyrate was demonstrated to have significant pharmacological and dietary potential as a therapeutic for the brain (59).There are no specific fruits and vegetables recommendations for patients with MS beyond the Dietary Guidelines for Americans (DGA), however, the risk for relapse decreased by 50% when a cup of vegetables is added (60). Ghadirian et al. (1998) showed the protective effect of some nutrients, such as vegetable protein, dietary and cereal fibers (61). In contrast, Zhang et al. (2001) reported no correlation between intake of fruits and vegetables, and the risk of MS in women (62).

Consumption of more non-starchy vegetables, resistant starch and soluble fibers together with fermented foods were suggested to reduce constipation, as a common symptom in patients with MS (63). Dark-green leafy vegetables are excellent sources of vitamin K and carotenoids that are involved in sphingolipid metabolism, enhanceing remyelination, cell membranes, and oligodendrocyte precursor cells (64). The Carotenoids in dark-green leafy vegetables are precursors to retinol (vitamin A) that improve the balance between Th17 cells and T Regulatory cells and are considered an important target in control of MS disease activity (65). Vegetables such as cabbage, onion and culinary mushrooms are rich sources of organic sulphur that can protect from neuroinflammation and/or neurodegeneration and result in favorable immunomodulation (66).

Deeply pigmented vegetables have higher polyphenol and antioxidant contents (67) that have anti-inflammatory and immune modulating properties (68) and can decrease the risk of cognitive decline (69), and neurodegeneration (70). Consumption of white fruits and vegetables including potatoes, bananas, apples, and pears is discouraged in patients with MS (71). White potatoes, tomatoes, eggplant and peppers as members of the nightshade (Solanaceae) family contain lectins and alkaloids, that can crossreact with autoantibodies and increase the disease activity (72). So elimination of nightshades may decrease inflammation and reduce brain symptoms (72).

As increased intestinal permeability occurs in MS, consumption of large amounts of lectins can damage the gut lining and increase the intestinal

permeability, thus permitting bacterial fragments such as lipopolysaccharide (LPS) and incompletely digested food proteins to enter the blood stream and trigger an immune response potentially culminating in MS disease (73). Vegetables and fruits plus a low fat diet and starchy foods such as grains, tubers, and legumes were advocated in MS patients (74). Legumes including soymilk, soybeans, green beans, dried beans, peas, peanuts are allowed as a Swank diet if they are counted towards the daily oil allowance, but they are excluded based on the WahlsElim diet and are also typically avoided on a Paleobecause of the high amounts of lectins (75).

There are not enough evidences to assess the effect of gluten on MS (76). The ESPEN does not currently recommend a gluten-free diet for prevention of MS (39). Whole grains were shown to be good fiber sources and beneficial for MS patients (17). In MS patients, it was shown that individuals in the top quintile of whole grain intake had lower odds of severe disability than individuals in the lowest quintile (77). Swank did not suggest avoidance of seaweed or algae intake as they are low in saturatedfat and would not be contraindicated on the diet (78). Yeast has a low saturated fat and is permittedin a Swank diet, but is not suggested regularly. A glassof skim milk with one tablespoon (9 g) nutritional yeast as an afternoon snack has been allowed. Regular consumption of nutritional yeast is recommended in WahlsElim diet to promote the Bvitamin content of the diet (36).

Protein Intake and MS

There are no specific protein recommendations for patients with MS (79). Meat and fish are suggested as they contain all essential amino acids, while most other sources of protein such as grains, legumes, dairy, and eggs are removed from the diet (80). Grass fed and finished meats, wild game and caught fish and shellfish are rich sources of omega-3 fatty acids and are encouraged to increase the intake of EPA and DHA (81). Organ meat diet consumption is encouraged, especially for liver to increase nutrient intake and prevent deficiency as they are excellent sources of B vitamins, vitamins A and D, phosphorus, zinc, selenium, copper, manganese, retinol which are important in bone metabolism, immune cellfunction, cell differentiation, choline and coenzyme Q10 (82). Fat-free and low-fat dairy products included in the DGA (24) are good sources of calcium, vitamin D, potassium and vitamin A and their roles in the development and treatment of MS are unclear (17). A recent study in MS patients denoted to the reduced risk for MS with low-fat dairy consumption > five times per week (83), but there may be allergic responses to milk consumption with saturated fat in patients with MS (84). Ghadirian et al. (1998) showed the protective effect of some nutrients, such as vegetable proteins too (61).

Multivitamins and Minerals and MS

Vitamin D, provided from ultraviolet B rays in the skin, is the other factor with an important role in calcium homeostasis, bone health, immunomodulatory effects and reduction in markers of oxidative stress (85). The results of vitamin D supplementation in MS patients have still been rather inconsistent with both positive (86) and no-effect results after supplementation (87). The deficiency of this vitamin D happens in majority of MS patients with seasonal variations and with an inverse association between serum vitamin D level and the seasonal risk of MS relapse (88). The combined effect of vitamin D supplementation, calorie-restriction, a semi-vegetarian diet and other dietary supplements (fish oil, lipoic acid, omega-3 polyunsaturated fatty acids, resveratrol and multivitamin complex) was shown without any significant changes in neurological signs of MS after 6 months (89).

Swank has suggested use of multivitamins A, D, C and B complex in the disease (33). He recommended 1000 mg vitamin C and 400 IU vitamin E, because of the antioxidant properties preventing the oxidation of unsaturated fats (36). WahlsElim supplemented multivitamins and minerals without any iron because an iron excess resulted in a higher risk of neurodegeneration (90). In MS patients, vitamin D levels <40 ng/mL lead to a higher risk of relapse and enhancing lesions (91). ESPEN has suggested intake of sufficient vitamin D for prevention of MS (39). Swank recommended vitamin D supplement in cod liver oil and in multivitamin capsules. In WahlsElim diet, 5000 IU of vitamin D3 has been suggested (91). The restriction of salt consumption to improve MS disease course is still controversial (92). Na intake in humans was not shown to be predictive of MS disease activity (93). Swank did not specifically suggested the use or restriction of salt, however, cola soft drinks were restricted to 491 g/day because of its Na content (36). Salt was not restricted in WahlsElim diet, but Paleo diets are typically lower in Na (94). Ghadirian et al. (1998) showed the protective effect of some nutrients, such as thiamine, riboflavin, vitamin C, calcium, and potassium (61).

Calorie and MS

Obesity during childhood was mentioned to increase the risk of developing MS and the risk of brain volume loss (95). Individuals with MS may

also be at risk when they have difficulty consuming adequate energy and nutrition (39). An increased risk of MS was noted with high energy and animal food intake (61). Swank found that MS patients lost weight because of reduced energy intake and the underweight patients achieved better outcomes (33, 35). Regarding sweeteners that are associated with unhealthy blood lipid levels, they increase dietary energy, carbohydrate and glycemic index, but are low in micronutrients (96). DGA has encouraged limited sugars to <10% of energy (24) to prevent excess energy intake. Swank suggested limitation in high sugar foods such as sugar, jelly, honey, and maple syrup as they can increase nervousness (36). Artificial sweeteners are inhibited as they can disrupt the microbiome, decrease satiety and result in weight gain (97).

Alcohol and MS

There are no specific alcohol recommendations for patients with MS. The DGA maximum alcohol intake for adults in women was recommended one drink per day and for men two drinks per day (24) In patients with MS, alcohol intake of >3 glasses red wine or >4 drinks per week was associated with more brain lesions, but with reduced disability and disease severity scores (98). Regular consumption of alcohol was demonstrated to be associated with reduced disability progression in individuals with relapsing-remitting MS, but not progressive form of disease (99). Swank suggested a maximum of one alcoholic beverage per day (58).

Caffeine and MS

No specific caffeine intake guidelines have been recommended yet for patients with MS (100). Swank restricted caffeine intake to three cups per day because of anxiety and nervousness observed in MS patients which exacerbated other MS-related symptoms and personal relationships (36).

Conclusion

Nutrition as simple and relatively low risk dietary intervention methods has an important role in improving outcomes in patients with MS. However, more long term and well defined studies are needed to confirm the effectiveness of diet to reduce severity and duration of relapses, the rate of progression and the deterioration to lower relapse rate. It seems that foods rich in fibers, supplementation with lipoic acid and vitamin D and a decrease in intake of saturated animal fats may be beneficial in MS patients.

Conflict of Interest

None declared.

References

1 Hadgkiss EJ, Jelinek GA, Weiland TJ, et al. The association of diet with quality of life, disability, and relapse rate in an international sample of people with multiple sclerosis. *Nutr Neurosci*. 2015;18:125-36.DOI:10.1179/1476830514Y.0000000117. PMID:24628020.

2 Wu H, Zhao M, Yoshimura A, et al. Critical link between epigenetics and transcription factors in the induction of autoimmunity: a comprehensive review. *Clin Rev Allergy Immunol*. 2016;50:333-44. DOI:10.1007/s12016-016-8534-y. PMID:26969025.

3 Olsson T, Barcellos LF, Alfredsson L. Interactions between genetic, lifestyle and environmental risk factors for multiple sclerosis. *Nat Rev Neurol*. 2017;13:25-36. DOI:10.1038/nrneurol.2016.187. PMID: 27934854.

4 Penesová A, Dean Z, Kollár B, et al. Nutritional intervention as an essential part of multiple sclerosis treatment? *Physiol Res*. 2018;67:521-533.PMID:29750884.

5 Saresella M, Mendozzi L, Rossi V, 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.DOI:10.3389/fimmu.2017.01391. PMID:29118761.

6 Dos Passos GR, Sato DK, Becker J, et al. Th17 Cells Pathways in Multiple Sclerosis and NeuromyelitisOptica Spectrum Disorders: Pathophysiological and Therapeutic Implications. *Mediators Inflamm*. 2016;2016:5314541. DOI:10.1155/2016/5314541. PMID:26941483.

7 Pierrot-Deseilligny C, Souberbielle JC. Vitamin D and multiple sclerosis: An update. *Mult Scler Relat Disord*. 2017;14:35-45. DOI:10.1016/j.msard.2017.03.014.PMID:28619429.

8 Dendrou CA, Fugger L, Friese MA. Immunopathology of multiple sclerosis. *Nat Rev Immunol*. 2015;15:545-58. DOI:10.1038/nri3871. PMID:26250739.

9 Storoni M, Plant GT. The Therapeutic Potential of the Ketogenic Diet in Treating Progressive Multiple Sclerosis. *Mult Scler Int*. 2015;2015:681289. DOI:10.1155/2015/681289. PMID:26839705.

10 Evans C, Beland SG, Kulaga S, et al. Incidence and prevalence of multiple sclerosis in the Americas: a systematic review. *Neuroepidemiology*. 2013;40:195-210. DOI:10.1159/000342779. PMID:23363936.

11 Grytten N, Torkildsen Ø, Myhr KM. Time trends in the incidence and prevalence of multiple

sclerosis in Norway during eight decades. *Acta Neurol Scand*. 2015;132:29-36. DOI:10.1111/ane.12428. PMID:26046556.

12 Browne P, Chandraratna D, Angood C, et al. Atlas of Multiple Sclerosis 2013: A growing global problem with widespread inequity. *Neurology*. 2014;83:1022-4. DOI:10.1212/WNL.0000000000000768. PMID:25200713.

13 Kingwell E, Marriott JJ, Jetté N, et al. Incidence and prevalence of multiple sclerosis in Europe: a systematic review. *BMC Neurol*. 2013;13:128. DOI:10.1186/1471-2377-13-128.PMID:24070256.

14 Roman C, Menning K. Treatment and disease management of multiple sclerosis patients: A review for nurse practitioners. *J Am Asso Nurse Pract*. 2017;29:629-38.DOI:10.1002/2327-6924.12514. PMID:29029375.

15 Marck CH, De Livera AM, Brown CR,e al. Health outcomes and adherence to a healthy lifestyle after a multimodal intervention in people with multiple sclerosis: Three year follow-up. *PLoS One*. 2018;13:e0197759.DOI:10.1371/journal.pone.0197759. PMID:29791509.

16 Esposito S, Bonavita S, Sparaco M, et al. The role of diet in multiple sclerosis: A review.. 2018;21:377-90.DOI:10.1080/1028415X.2017.1303016. PMID:28338444.

17 Katz Sand I. The Role of Diet in Multiple Sclerosis: Mechanistic Connections and Current Evidence. *Curr Nutr Rep*. 2018;7:150-60.DOI:10.1007/s13668-018-0236-z. PMID:30117071.

18 Yadav V, Marracci G, Kim E, et al. Low-fat, plant-based diet in multiple sclerosis: A randomized controlled trial. *Mult Scler Relat Disord*. 2016;9:80-90. DOI:10.1016/j.msard.2016.07.001. PMID:27645350.

19 Swank RL, Goodwin J. Review of MS patient survival on a Swank low saturated fat diet. *Nutrition*. 2003;19:161-2. DOI:10.1016/s0899-9007(02)00851-1. PMID:12591551.

20 Fitzgerald KC, Vizthum D, Henry-Barron B, et al. Effect of intermittent vs. daily calorie restriction on changes in weight and patient-reported outcomes in people with multiple sclerosis. *Mult Scler Relat Disord.* 2018;23:33-9.DOI:10.1016/j.msard.2018.05.002. PMID:29753994.

21 Irish AK, Erickson CM, Wahls TL, et al. Randomized control trial evaluation of a modified Paleolithic dietary intervention in the treatment of relapsing-remitting multiple sclerosis: a pilot study. *Degener Neurol Neuromuscul Dis*. 2017;7:1-18.DOI:10.2147/DNND.S116949. PMID:30050374.

22 Wahls TL, Chenard CA, Snetselaar LG. Review of two popular eating plans within the multiple sclerosis community: low saturated fat and modified paleolithic. *Nutrients*. 2019;11pii:E352. DOI:10.3390/nu11020352. PMID:30736445.

23 Venasse M, Edwards T, Pilutti LA. Exploring Wellness Interventions in Progressive Multiple Sclerosis: an Evidence-Based Review. *Curr Treat Options Neurol*. 2018;20:13.DOI:10.1007/s11940-018-0497-2. PMID:29637453.

24 US Department of Health and Human Services and U.S. Department of Agriculture. 2015-2020 Dietary Guidelines for Americans; Skyhorse Publishing Inc.: Washington, DC, USA; 2015.

25 Diet & Nutrition. https://www.nationalmssociety.org/Living-Well-With-MS/Diet-Exercise-Healthy-Behaviors/Diet-Nutrition#section-0. Accessed 16 October, 2017.

26 Eckel RH, Jakicic JM, Ard JD, et al. 2013 AHA/ACC Guideline on Lifestyle Management to Reduce Cardiovascular Risk: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;129:S76–S99.DOI:10.1161/01.cir.0000437740.48606.d1. PMID:24222015.

27 Kushi LH, Doyle C, McCullough M,et al. American Cancer Society Guidelines on nutrition and physical activity for cancer prevention: reducing the risk of cancer with healthy food choices and physical activity. *CA Cancer J Clin*. 2012;62:30-67. DOI:10.3322/caac.20140. PMID:22237782.

28 Swank RL. Multiple sclerosis; a correlation of its incidence with dietary fat. *Am J Med Sci*. 1950;220:421-30. DOI:10.1097/00000441-195022040-00011. PMID:14771073.

29 Zhornitsky S, Mckay KA, Metz LM, et al. Cholesterol and markers of cholesterol turnover in multiple sclerosis: relationship with disease outcomes. *Mult Scler Relat Disord*. 2016;5:53-65.DOI:10.1016/j.msard.2015.10.005. PMID:26856944.

30 Esparza ML, Sasaki S, Kesteloot H. Nutrition, latitude, and multiple sclerosis mortality: an ecologic study. *Am J Epidemiol.* 1995;142:733-7.DOI:10.1093/oxfordjournals.aje.a117704. PMID:7572944.

31 Das UN. The lipids that matter from infant nutrition to insulin resistance. *Prostaglandins Leukot Essent Fatty Acids*. 2002;67:1-12. DOI:10.1054/plef.2002.0374. PMID:12213429.

32 Kumar GS, Das UN. Effect of prostaglandins and their precursors on the proliferation of human lymphocytes and their secretion of tumor necrosis factor and various interleukins. *Prostaglandins Leukot Essent Fatty Acids*. 1994;50:331-4.DOI:10.1016/0952-3278(94)90242-

9. PMID:7938085.
33 Swank RL. Treatment of multiple sclerosis with low-fat diet. *AMA Arch NeurolPsychiatr.* 1953;69:91-103. PMID:12996138.
34 Swank RL. Treatment of multiple sclerosis with low-fat diet; results of five and one-half years' experience. *AMA Arch Neurol Psychiatr.* 1955;73:631-44. DOI:10.1001/archneurpsyc.1955.02330120035004. PMID:14375427.
35 Swank RL. Multiple sclerosis: twenty years on low fat diet. *Arch Neurol.* 1970;23:460-74.
36 Swank RL, Dugan BB. The Multiple Sclerosis Diet Book. A Low-Fat Diet for the Treatment of M.S. Doubleday: New York, New York; 1987.
37 Swank RL. Treatment of multiple sclerosis with a low-fat diet. *J Am Diet Assoc.* 1960;36:322-5. PMID:13836031.
38 Institute of Medicine. Dietary Reference Intakes: Macronutrients.http://www.nationalacademies.org/hmd/~/media/Files/Activity%20Files/Nutrition/DRITables/8_Macronutrient%20Summary.pdf?la=en. Accessed 16 June, 2018.
39 Burgos R, Breton I, Cereda E, et al. ESPEN guideline clinical nutrition in neurology. *Clin. Nutr.* 2018;37:354-96.DOI:10.1016/j.clnu.2017.09.003. PMID:29274834.
40 Khalatbary AR. Olive oil phenols and neuroprotection. *Nutr Neurosci.* 2013;16:243-9. DOI:10.1179/1476830513Y.0000000052. PMID:23406576.
41 Wergeland S, Torkildsen O, Bo L, et al. Polyunsaturated fatty acids in multiple sclerosis therapy. *Acta Neurol Scand Suppl.* 2012;126:70-5. DOI:10.1111/ane.12034. PMID:23278660.
42 Holman RT, Johnson SB, Kokmen E. Deficiencies of polyunsaturated fatty acids and replacement by nonessential fatty acids in plasma lipids in multiple sclerosis. *Proc Natl Acad Sci USA.* 1989;86:4720-4.PMID:2734316.
43 Hoare S, Lithander F, Van Der Mei I, et al. Higher intake of omega-3 polyunsaturated fatty acids is associated with a decreased risk of a first clinical diagnosis of central nervous system demyelination: results from the Ausimmune Study. *Mult Scler.* 2016;22:884-92. DOI:10.1177/1352458515604380. PMID:26362904.
44 Salinthone Salinthone S, Yadav V, Schillace RV, et al. Lipoic acid attenuates inflammation via cAMP and protein kinase A signaling. *PLoS One.* 2010;5:e13058. DOI:10.1371/journal.pone.0013058. PMID:20927401.
45 Schreibelt G, Musters RJ, Reijerkerk A, et al. Lipoic acid affects cellular migration into the central nervous system and stabilizes blood-brain barrier integrity. *J Immunol.* 2006;177:2630-7.DOI:10.4049/jimmunol.177.4.2630. PMID:16888025.
46 Nightingale S, Woo E, Smith AD, et al. Red blood cell and adipose tissue fatty acids in mild inactive multiple sclerosis. *Acta Neurol Scand.* 1990;82:43-50.DOI:10.1111/j.1600-0404.1990.tb01586.x. PMID:2239137.
47 Farinotti M, Vacchi L, Simi S, et al. Dietary interventions for multiple sclerosis. *Cochrane Database Syst Rev.*2012;12:CD004192. DOI:10.1002/14651858.CD004192.pub3. PMID:23235605.
48 Kong-Gonzalez M, Perez-Cortez JG, Hernandez-Giron C, et al. Polyunsaturated fatty acids for multiple sclerosis treatment: scientific evidence (in Spanish). *Medwave.* 2015;15:e6062.DOI:10.5867/medwave.2015.01.6062. PMID:25628005.
49 Ramirez-Ramirez V, Macias-Islas MA, Ortiz GG, et al. Efficacy of fish oil on serum of TNF alpha, IL-1 beta, and IL-6 oxidative stress markers in multiple sclerosis treated with interferon beta-1b. *Oxid Med Cell Longev.* 2013;2013:09493. DOI:10.1155/2013/709493.PMID:23861993.
50 Nordvik I, Myhr Km, Nyland H, et al. Effect of dietary advice and n-3 supplementation in newly diagnosed MS patients. *Acta Neurol Scand.* 2000;102:143-9.DOI:10.1034/j.1600-0404.2000.102003143.x. PMID:10987373.
51 Bates D, Cartlidge NE, French JM, et al. A double-blind controlled trial of long chain n-3 polyunsaturated fatty acids in the treatment of multiple sclerosis. *J Neurol Neurosurg Psychiatry.* 1989;52:18-22.DOI:10.1136/jnnp.52.1.18. PMID:2540285.
52 Gallai V, Sarchielli P, Trequattrini A, et al. Supplementation of polyunsaturated fatty acids in multiple sclerosis. *Ital J Neurol Sci.*1992;13:401-7. DOI:10.1007/bf02312146. PMID:1517064.
53 Rezapour-Firouzi S, Arefhosseini SR, Ebrahimi-Mamaghani M, et al. Alteration of delta-6-desaturase (FADS2), secretory phospholipase-A2 (sPLA2) enzymes by Hot-nature diet with co-supplemented hemp seed, evening primrose oils intervention in multiple sclerosis patients. *Complement Ther Med.*2015;23:652-7. DOI:10.1016/j.ctim.2015.07.003. PMID:26365444.
54 Riemann-Lorenz K, Eilers M, Von Geldern G, et al. Dietary interventions in multiple sclerosis: development and pilot-testing of an Evidence Based Patient Education Program. *PLoS One.*2016;11:e0165246. DOI:10.1371/journal.pone.0165246. PMID:27764237.
55 Bjornevik K, Chitnis T, Ascherio A, et al. Polyunsaturated fatty acids and the risk of

multiple sclerosis. *Mult Scler*. 2017;23:1830-8. PMID:28156186. DOI:10.1177/1352458517691150.

56 Riccio P, Rossano R. Diet, Gut Microbiota, and Vitamins D + A in Multiple Sclerosis. *Neurotherapeutics*. 2018;15:75-91.DOI:10.1007/s13311-017-0581-4. PMID:29067566

57 Center for Nutrition Policy and Promotion. Healthy US-Style Pattern: Recommended Intake Amounts. https://www.cnpp.usda.gov/sites/default/files/usda_food_patterns/HealthyUSStylePattern-RecommendedIntakeAmounts.pdf. Accessed 19 September, 2017.

58 Swank MS Foundation. The Swank Low-Fat Diet for the Treatment of MS. http://www.swankmsdiet.org/the-diet/.Accessed 17 October, 2017.

59 Priebe MG, Wang H, Weening D, et al. Factors related to colonic fermentation of nondigestible carbohydrates of a previous evening meal increase tissue glucose uptake and moderate glucose-associated inflammation. *Am J Clin Nutr*. 2010;91:90-7. DOI:10.3945/ajcn.2009.28521. PMID:19889821.

60 Azary S, Schreiner T, Graves J, et al. Contribution of dietary intake to relapse rate in early paediatric multiple sclerosis. *J Neurol Neurosurg Psychiatry*. 2018;89:28-33.DOI:10.1136/jnnp-2017-315936. PMID:28993476.

61 Ghadirian P, Jain M, Ducic S, et al. Nutritional factors in the aetiology of multiple sclerosis: a case-control study in Montreal, Canada. *Int J Epidemiol*. 1998;27:845-52. DOI:10.1093/ije/27.5.845. PMID:9839742.

62 Zhang SM, Hernan MA, Olek MJ, et al. Intakes of carotenoids, vitamin C, and vitamin E and MS risk among two large cohorts of women. *Neurology*. 2001;57:75-80. DOI:10.1212/wnl.57.1.75.PMID:11445631.

63 Coggrave M, Norton C. Management of faecal incontinence and constipation in adults with central neurological diseases. *Cochrane Database Syst Rev*. 2013;12:CD002115. DOI:10.1002/14651858.CD002115.pub4. PMID:24347087.

64 Popescu DC, Huang H, Singhal NK,et al. Vitamin K enhances the production of brain sulfatides during remyelination. *PLoS One*. 2018;13:e0203057.PMID:30148869. DOI:10.1371/journal.pone.0203057.

65 Raverdeau M, Breen CJ, Misiak A, et al. Retinoic acid suppresses IL-17 production and pathogenic activity of gammadelta T cells in CNS autoimmunity. *Immunol Cell Biol*. 2016;94:763-73.DOI:10.1038/icb.2016.39. PMID:27089940.

66 Masci A, Mattioli R, Costantino P, et al. Neuroprotective Effect of Brassica oleracea Sprouts Crude Juice in a Cellular Model of Alzheimer's Disease. *Oxid Med Cell Longev*. 2015;2015:781938.DOI:10.1155/2015/781938. PMID:26180595.

67 Keservani RK, Sharma AK, Kesharwani RK. Medicinal Effect of Nutraceutical Fruits for the Cognition and Brain Health. *Scientifica*. 2016;2016:3109254.DOI:10.1155/2016/3109254. PMID:26966612.

68 Corbi G, Conti V,Davinelli S,et al. Dietary Phytochemicals in Neuroimmunoaging: A New Therapeutic Possibility for Humans? *Front Pharmacol*. 2016;7:364.PMID:27790141. DOI:10.3389/fphar.2016.00364.

69 Panickar KS, Jang S. Dietary and plant polyphenols exert neuroprotective effects and improve cognitive function in cerebral ischemia. *Recent Pat Food Nutr Agric*. 2013;5:128-43. DOI :10.2174/1876142911305020003. PMID:23621667.

70 Islam MA, Khandker SS, Alam F, et al. Alzheimer's Disease and Natural Products: Future Regimens Emerging from Nature. *Curr Top Med Chem*. 2017;17:1408-28. DOI:10.2174/1568026617666170103163054. PMID:28049401.

71 Denis MC, Roy D,Yeganeh PR, et al. Apple peel polyphenols: a key player in the prevention and treatment of experimental inflammatory bowel disease. *Clin Sci (Lond.)* 2016;130:2217-37. DOI:10.1042/CS20160524. PMID:27630205.

72 Vojdani A. Lectins, agglutinins, and their roles in autoimmune reactivities. *Altern Ther Health Med*. 2015;21:46–51.PMID:25599185.

73 Buscarinu MC, Romano S, Mechelli R, et al. Intestinal Permeability in Relapsing-Remitting Multiple Sclerosis. *Neurotherapeutics*. 2018;15:68-74.DOI:10.1007/s13311-017-0582-3. PMID:29119385.

74 McDougall J, Thomas LE, McDougallC,et al. Effects of 7 days on an ad libitum low-fat vegan diet: the McDougall Program cohort. *Nutr J*. 2014;13:99.DOI:10.1186/1475-2891-13-99. PMID:25311617.

75 Cordain L. The Paleo Diet. http://thepaleodiet.com/. Accessed 01 September, 2018.

76 Thomsen HL, Jessen EB, Passali M, et al. The role of gluten in multiple sclerosis: A systematic review. *MultSclerRelatDisord*. 2019;27:156-63.DOI:10.1016/j.msard.2018.10.019. PMID:30384202.

77 Fitzgerald KC, Tyry T, Salter A, et al. Diet quality is associated with disability and symptom severity in multiple sclerosis. *Neurology*. 2018;90:e1–e11. DOI:10.1212/WNL.0000000000004768. PMID:29212827

78 Pereira L. A review of the nutrient composition of selected edible seaweeds. In Seaweed; Pomin VH, Nova Science Publishers, Inc.: Hauppauge, NY, USA; 2011.p.15-47.
79 Grimstad T, Berge RK , Bohov P, et al. Salmon diet in patients with active ulcerative colitis reduced the simple clinical colitis activity index and increased the anti-inflammatory fatty acid index-A pilot study. *Scand J Clin Lab Invest*. 2011;71:68-73. DOI:10.3109/00365513.2010.542484. PMID:21142420.
80 Yin J, Ren W, Huang X,et al. Protein restriction and cancer. *Biochim Biophys Acta*. 2018;1869:256–262.DOI:10.1016/j.bbcan.2018.03.004.PMID:29596961.
81 Wood JD, Enser M, Fisher AV, et al. Fat deposition, fatty acid composition and meat quality: A review. *Meat Sci*. 2008;78:343-58.DOI:10.1016/j.meatsci.2007.07.019. PMID:22062452.
82 Ercan P, El SN. Changes in content of coenzyme Q10 in beef muscle, beef liver and beef heart with cooking and in vitro digestion. *J Food Comp Analysis*. 2011;24:1136-40. DOI:10.1016/j.jfca.2011.05.002.
83 Bagheri M, Maghsoudi Z, Fayazi S, et al. Several food items and multiple sclerosis: A case-control study in Ahvaz (Iran). *Iran J Nurs Midwifery Res*. 2014;19:659-65.PMID:25558266.
84 Tsabouri S, Douros K, Priftis KN.Cow's milk allergenicity. *Endocr Metab Immune Disord Drug Targets*. 2014;14:16-26.DOI:10.2174/1871530314666140121144224. PMID:24450454.
85 Dankers W, Colin EM, Van Hamburg JP, et al. Vitamin D in autoimmunity: molecular mechanisms and therapeutic potential. *Front Immunol*.2017;7:697. DOI:10.3389/fimmu.2016.00697. PMID:28163705.
86 Soilu-Hänninen M, Aivo J, Lindström BM, et al. A randomised, double blind, placebo controlled trial with vitamin D3 as an add on treatment to interferon β-1b in patients with multiple sclerosis. *J Neurol Neurosurg Psychiatr*.2012;83:565-71. DOI:10.1136/jnnp-2011-301876. PMID:22362918.
87 James E, Dobson R, Kuhle J, et al. The effect of vitamin Drelated interventions on multiple sclerosis relapses: a meta-analysis. *MultScler*. 2013;19:1571-9. DOI:10.1177/1352458513489756. PMID:23698130.
88 Hartl C, Obermeier V, Gerdes LA, et al. Seasonal variations of 25-OH vitamin D serum levels are associated with clinical disease activity in multiple sclerosis patients. *J Neurol Sci*. 2017;375:160-4.DOI:10.1016/j.jns.2017.01.059. PMID:28320120.
89 Riccio P, Rossano R, Larocca M, et al. Anti-inflammatory nutritional intervention in patients with relapsing-remitting and primary-progressive multiple sclerosis: a pilot study. *Exp Biol Med (Maywood)*.2016;241:620-35. DOI:10.1177/1535370215618462. PMID:26785711.
90 Chiabrando D, Fiorito V, Petrillo S, et al. Unraveling the Role of Heme in Neurodegeneration. *Front Neurosci*. 2018;12:712. DOI:10.3389/fnins.2018.00712. PMID:30356807.
91 Fitzgerald KC, Munger KL, Kochert K, et al. Association of Vitamin D Levels With Multiple Sclerosis Activity and Progression in Patients Receiving Interferon Beta-1b. *JAMA Neurol*. 2015;72:1458-65.DOI:10.1001/jamaneurol.2015.2742. PMID:26458124.
92 Pugliatti M. People with MS should consume a low-salt diet - Commentary. Mult Scler. 2016;22:1781-2.DOI:10.1177/1352458516669003. PMID:27609132.
93 Fitzgerald KC, Munger KL, et al. Sodium intake and multiple sclerosis activity and progression in benefit. *Ann Neurol*. 2017;82:20–29.DOI:10.1002/ana.24965. PMID:28556498.
94 Cordain L. The Nutritional Characteristics of a Contemporary Diet Based Upon Paleolithic Food Groups. *J Am Neutraceut Assoc*. 2002;5:15-24.
95 Mowry EM, Azevedo CJ, McCulloch CE, et al. Body mass index, but not vitamin D status, is associated with brain volume change in MS. *Neurology*. 2018;91:e2256-e2264.DOI:10.1212/WNL.0000000000006644. PMID:30429274.
96 Welsh JA, Sharma A, Abramson JL, et al. Caloric sweetener consumption and dyslipidemia among US adults. *JAMA*. 2010;303:1490-7.DOI:10.1001/jama.2010.449. PMID:20407058.
97 Pearlman M, Obert J, Casey L. The Association Between Artificial Sweeteners and Obesity. *Curr Gastroenterol Rep*. 2017;19:64.DOI:10.1007/s11894-017-0602-9. PMID:29159583.
98 Diaz-Cruz C, Chua AS, Malik MT, et al. The effect of alcohol and red wine consumption on clinical and MRI outcomes in multiple sclerosis. *Mult Scler Relat Disord*. 2017;17:47-53. DOI:10.1016/j.msard.2017.06.011. PMID:29055473.
99 D'Hooghe MB, Haentjens P, Nagels G, et al. Alcohol, coffee, fish, smoking and disease progression in multiple sclerosis. *Eur J Neurol*. 2012:19:616-24.PMID:22117611. DOI:10.1111/j.1468-1331.2011.03596.x.
100 Tellone E, Galtieri A, Russo A, Ficarra S. Protective effects of the caffeine against neurodegenerative diseases. *Curr Med Chem*. 2017. DOI:10.2174/0929867324666171009104040. PMID:28990513.