REVIEW

Influence of Diet in Multiple Sclerosis: A Systematic Review[1,2]

M José Bagur,[3] M Antonia Murcia,[4,5] Antonia M Jiménez-Monreal,[4,5] Josep A Tur,[5,6] M Mar Bibiloni,[5,6] Gonzalo L Alonso,[3] and Magdalena Martínez-Tomé,[4,5]*

[3]*Department Science and Technology and Genetics Agroforestal, University of Castilla La-Mancha, Campus Universitario, Albacete, Spain;* [4]*Department of Food Science, Regional Campus of International Excellence "Campus Mare Nostrum," University of Murcia, Murcia, Spain;* [5]*CIBEROBN CB12/03/30038 (Physiopathology of Obesity and Nutrition), Instituto de Salud Carlos III, Madrid, Spain; and* [6]*Research Group on Community Nutrition and Oxidative Stress, University of the Balearic Islands, Palma de Mallorca, Spain*

ABSTRACT

Nutrition is considered to be a possible factor in the pathogenesis of the neurological disease multiple sclerosis (MS). Nutrition intervention studies suggest that diet may be considered as a complementary treatment to control the progression of the disease; a systematic review of the literature on the influence of diet on MS was therefore conducted. The literature search was conducted by using Medlars Online International Literature (MEDLINE) via PubMed and Scopus. Forty-seven articles met the inclusion criteria. The reviewed articles assessed the relations between macro- and micronutrient intakes and MS incidence. The patients involved used alternative therapies (homeopathy), protocolized diets that included particular foods (herbal products such as grape seed extract, ginseng, blueberries, green tea, etc.), or dietary supplements such as vitamin D, carnitine, melatonin, or coenzyme Q10. Current studies suggest that high serum concentrations of vitamin D, a potent immunomodulator, may decrease the risk of MS and the risk of relapse and new lesions, while improving brain lesions and timed tandem walking. Experimental evidence suggests that serum vitamin D concentration is lower during MS relapses than in remission and is associated with a greater degree of disability [Expanded Disability Status Scale (EDSS) score >3]. The findings suggest that circulating vitamin D concentrations can be considered a biomarker of MS and supplemental vitamin D can be used therapeutically. Other studies point to a negative correlation between serum vitamin B-12 concentrations and EDSS score. Vitamin B-12 has fundamental roles in central nervous system function, especially in the methionine synthase–mediated conversion of homocysteine to methionine, which is essential for DNA and RNA synthesis. Therefore, vitamin B-12 deficiency may lead to an increase in the concentration of homocysteine. Further research is clearly necessary to determine whether treatment with vitamin B-12 supplements delays MS progression. *Adv Nutr* 2017;8:463–72.

Keywords: multiple sclerosis, diet, intake, food, nutrition, systematic review

Introduction

Multiple sclerosis (MS)[7] is a chronic inflammatory autoimmune disease of the central nervous system. The fact that its etiology is unknown may be partially attributed to its multifactorial nature. The role of nutritional factors in MS pathogenesis is still unclear, and the effect of nutritional intervention on inflammatory status and wellness in patients with MS has not been associated with any dietary pattern (1).

Reviews before 2005 showed that any possible relations between diet and MS were not subjected to adequate study, and the results that were available generally concerned macronutrients. However, it is now known that the intake of SFAs of animal origin must be controlled to avoid the increase in inflammatory processes in MS (1). There has been renewed interest among MS researchers in the therapeutic potential of a low-fat diet and PUFA supplementation, which may have some beneficial effects in the disease (2). A high BMI before the age of 20 y has been associated with a significantly increased risk of MS (1).

The role of minerals, trace elements, antioxidants, and vitamins, which has received increased attention in the past decade, is unclear. For example, an increased risk of MS in patients with vitamin D insufficiency may explain the strong latitude gradient in MS prevalence. Higher vitamin D

[1] Supported by the Spanish Ministry of Health and Consumption Affairs (projects 05/1276, 08/1259, 11/01791, and 14/00636; Red Predimed-RETIC RD06/0045/1004; and CIBEROBN CB12/03/30038), grants 35/2011 and 23/2012 (Balearic Islands Government), and European Union Fondo Europeo Desarrollo Regional funds.
[2] Author disclosures: MJ Bagur, MA Murcia, AM Jiménez-Monreal, JA Tur, MM Bibiloni, GL Alonso, and M Martínez-Tomé, no conflicts of interest.
*To whom correspondence should be addressed. E-mail: mmtome@um.es.
[7] Abbreviations used: EDSS, Expanded Disability Status Scale; MeSH, Medical Subject Headings; MS, multiple sclerosis; 8-iso-PGF2α, 8-iso-prostaglandin F2α.

©2017 American Society for Nutrition.

concentrations appear to slow disease progression (3). It is still unknown whether dietary antioxidants have additional biological properties beyond simple antioxidant activity in MS. The reason for using antioxidants in MS and other autoimmune and inflammatory diseases is based on the observation that oxidative stress is one of the most important components of the inflammatory process, leading to the degradation of myelin and axonal damage (4). A recent study showed that nutritional intervention with anti-inflammatory foods and dietary supplements decreased the biological synthesis of proinflammatory compounds and made immunomodulatory drugs more effective, which improved the well-being of patients with MS (1).

Clinicians recommend that patients with MS, as well as individuals in general, should adopt a healthy diet, because studies have pointed to the protective function of given dietary patterns (5). Dietary habits that diminish MS symptoms may be considered as complementary treatments of MS. Likewise, further knowledge on the effects of possible harmful dietary habits could help prevent chronic states of inflammation and avoid worsening of the disease (6).

It is commonly accepted that nutrition is one of the possible environmental factors involved in the pathogenesis of MS, but its role as a complementary MS treatment is unclear and, to a large extent, ignored (7). Despite this, there are many patients who frequently use alternative therapies, diets, and dietary supplements (8–10). The aim of this study was to systematically review the literature published in the past decade (2005–2015) with regard to the influence of diet on MS.

Methods and Results

A systematic literature search was performed that covered publications up to September 2015. The databases used were Medlars Online International Literature (MEDLINE) via PubMed and Scopus. The Medical Subject Headings (MeSH) dictionary in PubMed was used to identify the keywords needed in the search. The terms used were "multiple sclerosis" [Major] AND ("diet" [MeSH] OR "intake" [MeSH] OR "nutrition" [MeSH] OR "food" [MeSH]). In total, 2839 articles (967 via PubMed and 1872 via Scopus) were selected (**Figure 1**). The selection was made by reading the title or abstract (carried out by MJB). Review articles, systematic reviews (1 article), duplicates (2 articles), and articles that did not meet the selection criteria were excluded. The selection criteria (3) consisted of articles on randomized trials, observational and experimental studies, dietary patterns that compared a specific dietary intervention, and diet plans or dietary supplementation with no dietary modification or placebo published between 2005 and 2015. Articles in languages other than English and Spanish were excluded.

In total, 314 articles (237 via PubMed, and 77 via Scopus) were selected for more detailed study. If the summaries did not contain sufficient data, a review of the full article was carried out to determine whether it met the inclusion criteria. Studies involving animal experiments or "in vitro" clinical trials, studies with a sample size <5 subjects, articles that reported on pharmacologic treatment, those that did not use validated methods to assess dietary intake, those addressing other neurological or autoimmune diseases, and those related to nonfood risk factors, such as additives or environmental contaminants, were excluded. After this process, 267 articles were rejected and 47 articles were chosen for review and discussion. Full-text articles were assessed by 2 of the authors (MJB and MM-T). Any disagreement was resolved by ≥2 of the reviewers (MAM, AMJ-M, MMB, and JAT).

The characteristics of the studies selected are shown in **Table 1** (5, 8–53), where they are grouped according to diet, FAs, or vitamins. Table 1 also provides a description of the 47 studies selected for this review, including the references, the method used, country, date of the survey, number of patients, sex, and age range. All of the articles were published between 2005 and 2015. The sample sizes varied from 9 (26) to 2303 (24) and included a higher number of women than men, although some studies did not report this fact. Of the 47 studies, 14 were European, 13 Iranian, and 9 were from the United States.

We reviewed 27 clinical trials and 20 observational studies. Most of the clinical trials had a control group. Population studies were supported by observational cohort studies, such as the Nurses' Health Study and the Nurses' Health Study II, and by self-administered questionnaires.

Diets

Seventeen of the articles reviewed referred to the characteristics of the patients' diet with regard to nutrients, malnutrition, or etiology (Table 1). Thirteen were observational studies and only 4 were clinical trials (16, 18, 19, 21). Six articles assessed the intake of macronutrients (5, 10, 11, 14–16), 1 study assessed the seasonal variations in intake (23), and 3 studies analyzed the use of alternative therapies together with diets and dietary supplements (8–10).

Dietary pattern and energy and nutrient intakes. Saka et al. (20) reported that the daily mean energy intakes of patients with MS were 2730 ± 841 kcal in men and 1967 ± 647 kcal in women. The total energy intake percentages of carbohydrates, protein, and fat were 46.9%, 14.6%, and 38.4%, respectively. Mohammad-Shirazi et al. (15) observed that protein and carbohydrate intakes in the studied population were less than recommended compared with DRIs, whereas their daily intakes of total and saturated fat were higher than reference values. Their intakes of polyunsaturated fat and dietary fiber were less than recommended (15). It has also been shown that a dietary pattern high in animal fat, meat products, hydrogenated fat, and sugars and low in whole grains was related to a higher prevalence of MS (13). This suggests a protective role for the consumption of fruit and vegetables and healthy fats and restricted meat consumption and important associations between healthy dietary habits and better physical and mental indicators (Multiple Sclerosis Quality of Life-54), accompanied by a lower level of disability (5, 11). Data from prospective studies in women (Nurses'

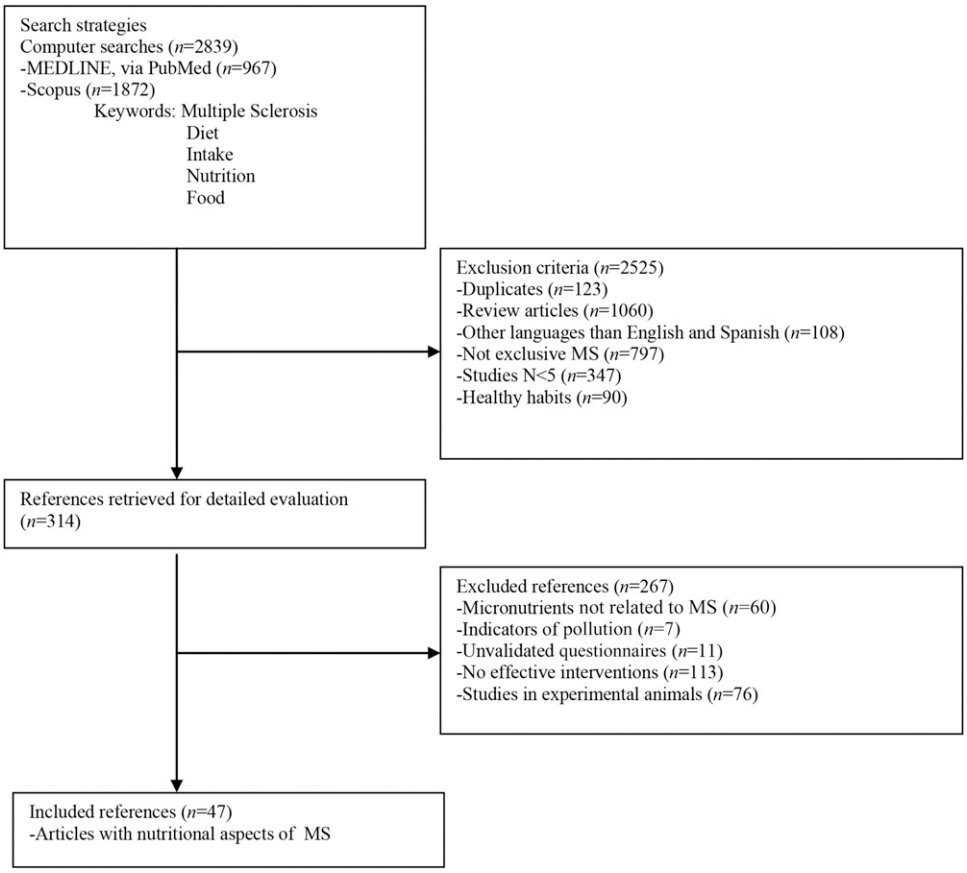

FIGURE 1 Flow diagram showing the literature search. MS, multiple sclerosis.

Health Study, Nurses' Health Study II) between 1986 and 1998 concerning lifestyle and medical conditions and another observational study conducted in 2005 showed no difference in alcohol consumption between the studied patients with MS and the general population (14, 17).

Seasonal variations. There is some evidence that individuals born in autumn have the lowest risk of developing MS, whereas those born in spring show the highest. It was suggested that seasonal changes in nutrient intake during pregnancy might affect fetal development at the cellular level and thus impact on the development of MS in later life of the offspring. Dietary data during pregnancy collected over 2.9 y by means of dietary questionnaires showed that the intakes of zinc, selenium, β-carotene, and vitamin C were lower in the summer. Individuals born in the spring would have been conceived in summer, which could explain the increased incidence of MS in those born during this season (23). The influence of lower intakes of certain micronutrients such as magnesium, calcium, and iron, as well as a high intake of sodium, may be related to the progression and activity of the disease in patients with secondary progressive MS (12, 18).

Malnutrition and clinical analysis. Patients with MS have a markedly lower mean BMI (a malnutrition indicator) than the recommended range, despite low levels of physical activity. This could be related to changes in metabolism after the onset of disease or muscular atrophy as a result of reduced muscle activity resulting from neuronal impairment (17). The prevalence of chronic malnutrition, based on a serum albumin <3.5 mg/dL, was 11.8% in patients with MS and only 2% in patients suffering other chronic diseases (22).

Clinical analyses have also been used to identify potential markers of the disease. It was found that patients with MS in a phase of clinical stability showed higher blood concentrations of total homocysteine and HDL cholesterol and lower blood concentrations of vitamin E and a lower vitamin E–to-cholesterol ratio (21).

Dietary supplements. Food supplements or dietary interventions in patients with MS are used frequently (64.7% of cases), with vitamins (81.8%), essential FAs (80.7%) and minerals (62.5%), and other herbal products such as blueberries, grape seed extract, ginkgo biloba, ginseng, St. John's wort, and valerian being used. Patients who consume supplements have more balanced diets (9). Patients with MS showed improved muscle metabolism and resistance to fatigue during moderate exercise if they consumed green tea catechins (16). There was no association between caffeine intake and MS risk (14). Other studies reflect the growing interest in alternative therapies such as homeopathy and acupuncture; the use of supplements such as coenzyme Q10, carnitine, and melatonin among others; and/or special diets, some of which are too restrictive for the health of the patients concerned (8–10).

TABLE 1 Descriptive analysis of the reviewed studies[1]

Study, year (ref)	Method	Country	Dietary assessment	Date of survey	Patients, *n*			Age range, y	Main results (in MS population)	Statistical tests applied
					M	F	Total			
Diet										
Bagheri et al., 2014 (11)	OT-C	Iran	FFQ	2012–2013	nd	nd	113	20–50	Reduction in risk for MS: fruit and low fat-dairy intake; increased risk of MS: solid vegetable oil intake	Chi-square, Fisher's test, logistic regression, multivariate logistic
Farez et al., 2015 (12)	OT	Argentina	Sodium intake estimated from sodium excretion in urine	nd	nd	nd	70	nd	Increased clinical disease activity: high sodium intake	Regression analysis
Hadgkiss et al., 2015 (5)	OT	Australia	DHQ: 24 items	nd	nd	nd	2087	>18	Lower level of disability (PDDS): higher fruit, vegetable, and unsaturated oils intake	Student's *t* test, chi-square, ANOVA, regression analysis
Jahromi et al., 2012 (13)	OT-C	Iran	FFQ: 168 items	nd	0	75	75	nd	Lower risk of MS development: low-fat dairy, whole grains, vegetable oil, and legumes intake; higher risk of MS development: animal fat and sugar intake	Multivariate logistic regression, Mantel-Haenszel, chi-square
Leong et al., 2009 (9)	OT	Australia	Self-administered questionnaire (minerals, vitamins, essential FAs, and others)	nd	121	291	416	nd	Vitamin, essential FA, and mineral supplement intakes in 64.7% of MS population	Chi-square
Massa et al., 2013 (14)	OT	USA	FFQ: 61 items	1980–2005	0	282	282	30–55	No effect on the risk of MS: alcohol and caffeine intake	Q-test
Masullo et al., 2015 (10)	OT	USA	24-h dietary recall questionnaire (ASA24: National Cancer Institute, 2011)	nd	3	32	35	>18	Lower antioxidant vitamin intake	Student's *t* test
Mohammad-Shirazi et al., 2007 (15)	OT	Iran	FFQ: 300 items; 24-h dietary recall questionnaire	2005	26	82	108	33.15[2]	Lower intake of protein, carbohydrate, PUFAs, and fiber and higher intake of saturated fats	Student's *t* test, Pearson correlation
Mähler et al., 2015 (16)	CT-C	Germany	—	nd	8	10	18	20–60	Improved efficiency of muscle work: green tea catechins	Wilcoxon
Norverdt et al., 2005 (17)	OT-C	Norway	Self-administered questionnaire	1997–1999	22	65	87	33[2]	No difference in alcohol consumption with general population and lower BMI in MS population	—
Ramsaransing et al., 2009 (18)	CT	Holland	14-d food diary (dietary counselor of the University Medical Center Groningen)	nd	27	53	80	nd	Lower intake of magnesium, calcium, and iron	Student's *t* test, ANOVA
Rezapour-Firouzi et al., 2014 (19)	CT-C	Iran	FFQ	2010–2011	34	66	100	14–55	Improved EDSS score with hemp seed and evening primrose oil intake	Paired *t* test
Saka et al., 2012 (20)	OT	Turkey	24-h dietary recall questionnaire (3 d) FFQ: nutrient databases (BEBIS); serum concentration	2011	15	22	37	nd	Lower intake of magnesium, calcium, iron, and zinc Negative correlation between serum vitamin B-12 concentration and EDSS score	Student's *t* test

(Continued)

TABLE 1 (*Continued*)

Study, year (ref)	Method	Country	Dietary assessment	Date of survey	Patients, *n*			Age range, y	Main results (in MS population)	Statistical tests applied
					M	F	Total			
Salemi et al., 2010 (21)	CT-C	Italy	Serum concentration	2004	20	20	40	16–58	Lower serum vitamin E concentration and vitamin E–to-cholesterol ratio	Mann-Whitney
Schwarz et al., 2008 (8)	OT	Germany	Self-administered questionnaire: 53 items	2007	409	1164	1573	40–56	Intake of dietary supplements (zinc, selenium, B vitamins) in >20% of MS population	Chi-square test, Fisher's test
Sorgun et al., 2014 (22)	OT-C	—	Serum concentration	2000–2012	24	78	102	19–70	Lower serum albumin concentration	Student's *t* test, Fisher's test
Watson and McDonald, 2007 (23)	OT	New Zealand	24-h diet record questionnaire (16 d over 2.9 y)	nd	0	214	214	18–35	Possible influence on MS of seasonal variation in nutrients during pregnancy	ANOVA
FAs										
Jelinek et al., 2013 (24)	OT	Australia	DHQ: 22 items (developed Australian cardiac population)	nd	407	1896	2303	>18	Frequent consumption of fish and ω-3 FA supplements associated with reduced disease activity and disability (PDDS)	ANOVA, ANCOVA
Kampman et al., 2007 (25)	OT	Norway	Self-administered questionnaire	2003–2004	55	97	152	6–20	Association of sun exposure and high fish intake with reduction in risk of developing MS	Chi-square, Mann-Whitney
Mauritz et al., 2013 (26)	CT	Spain	Serum concentration	nd	nd	nd	9	nd	Antioxidant supplementation increases catalase activity	Student's *t* test
Pantzaris et al., 2013 (27)	CT-C	Cyprus	—	2007	20	60	80	18–65	Reduced annual relapse rate and disability (EDSS) with PUFA and antioxidant vitamin supplementation	Kruskal-Wallis, Fisher's test
Rezapour-Firouzi et al., 2013 (28)	CT	Iran	Nonquantitative FFQ	2010–2011	34	66	100	14–55	Hemp seed and evening primrose oils increase PUFAs	Student's *t* test
Shinto et al., 2009 (29)	CT	USA	—	nd	1	9	10	18–65	ω-3 FA supplementation decreases metalloproteinase in RRMS	—
Weinstock-Guttman et al., 2005 (30)	CT-C	USA	—	nd	nd	nd	31	18–60	Low-fat dietary and fish-oil intake associated with lower number of relapses	—
Dörr et al., 2012 (31)	CT-C	Germany	Serum vitamin D concentration	2011–2012	nd	nd	80	18–65	Reduction in new lesions in MS with high-dose vitamin D supplement	—
Kampman et al., 2012 (32)	CT-C	Norway	Serum vitamin D concentration	2008–2010	11	24	35	18–50	Supplementation with vitamin D does not result in a reduction in relapse rate	Chi-square, Mann-Whitney, Student's *t* test
Kimball et al., 2007 (33)	CT	Canada	Serum vitamin D concentration	2003–2005	5	7	12	nd	Reduction in number of gadolinium-enhancing lesions with high-dose vitamin D supplement	Paired *t* test, Wilcoxon
Langer-Gould et al., 2011 (34)	OT	USA	Serum vitamin D concentration	2002–2005	0	28	28	nd	Low serum vitamin D: no risk factor for relapses in pregnant and lactating women	Chi-square, Fisher's test

(*Continued*)

TABLE 1 (*Continued*)

Study, year (ref)	Method	Country	Dietary assessment	Date of survey	Patients, *n*			Age range, y	Main results (in MS population)	Statistical tests applied
					M	F	Total			
Mazdeh et al., 2013 (35)	CT-C	Iran	Serum vitamin D concentration	nd	18	57	75	20–40	Low serum vitamin D concentration	Student's *t* test
McDowell et al., 2011 (36)	OT	USA	Retrospective recall questionnaire	nd	nd	nd	nd	6–15	Intake of cod liver oil associated with later onset of MS symptoms	Multivariate analyses
Mirzaei et al., 2011 (37)	OT	USA	Retrospective recall questionnaire: 24 food items	1989–2001	0	199	199	—	Higher vitamin D intake during pregnancy associated with reduction in risk of MS in offspring	Multiple linear regression model
Munger et al., 2006 (38)	OT	USA	Retrospective recall questionnaire, 24 items: HS-FFQ	1992–2004	148	74	222	18–48	Higher serum vitamin D concentration associated with lower risk of MS	Multivariate analyses
Munger et al., 2011 (39)	OT	USA	Retrospective recall questionnaire (HS-FFQ)	1976–2005	nd	801	801	25–55	Intake of vitamin D from multivitamins during adolescence not associated with MS risk	Multivariate analyses
Smolders et al., 2010 (40)	CT	Holland	—	2009	7	8	15	25–50	Higher dose of vitamin supplementation does not induce decompensation of calcium metabolism	Mann-Whitney, Wilcoxon
Soilu-Hänninen et al., 2005 (41)	CT-C	Finland	Serum vitamin D concentration	2000–2003	8	32	40	18–53	Lower vitamin D concentration during MS relapses than in remission	Multiple statistical analyses
Soilu-Hänninen et al., 2012 (42)	CT-C	Finland	—	nd	nd	nd	66	nd	Vitamin D added with therapy to interferon reduces MRI disease activity	—
Steffensen et al., 2011 (43)	CT	Norway	—	2007–2010	11	24	35	18–50	No reduction in risk of osteoporosis in MS: vitamin D supplement	Student's *t* test, chi-square
Toghianifar et al., 2015 (44)	CT-C	Iran	—	2013–2014	9	35	44	18–55	High dose of vitamin D reduces disease activity (EDSS)	Mann-Whitney, Wilcoxon
van der Mei et al., 2007 (45)	CT-C	Australia	Serum vitamin D concentration	nd	44	92	136	<60	Higher disability (EDSS >3) associated with vitamin D insufficiency and reduced exposure to sun	ANOVA
Wingerchuk et al., 2005 (46)	CT	USA	—	1999–2001	3	12	15	22–44	Oral calcitriol is safe and well tolerated in MS	Paired *t* test
Other vitamins										
Bitarafan et al., 2015 (47)	CT-C	Iran	—	2010–2012	25	76	101	20–45	Vitamin A supplement improves total MSFC score in RRMS but does not change relapse rate	Kolmogorov-Smirnov, independent-sample *t* test, Mann-Whitney
Hejazi et al., 2014 (48)	CT-C	Iran	FFQ, 24-h dietary recall questionnaire for 3 d	nd	6	1	37	18–52	No difference in dietary intake of vitamins A, C, and E and folate between MS and healthy subjects	ANOVA
Khalili et al., 2014 (49)	CT-C	Iran	—	nd	nd	nd	52	18–50	Supplementation with lipoic acid reduces cytokine profiles	—

(*Continued*)

TABLE 1 (*Continued*)

Study, year (ref)	Method	Country	Dietary assessment	Date of survey	Patients, *n*			Age range, y	Main results (in MS population)	Statistical tests applied
					M	F	Total			
Kocer et al., 2009 (50)	CT-C	Israel	Serum vitamin B-12 concentration	2004–2005	15	20	35	30.1[2]	Lower serum vitamin B-12 concentration	Student's *t* test, Mann-Whitney, chi-square test
Moghaddasi et al., 2013 (51)	CT-C	Iran	Serum concentrations	nd	18	57	75	31.97[2]	Lower serum vitamin B-12 and folate concentrations in patients with RRMS	Chi-square test, Pearson correlation
Najafi et al., 2012 (52)	CT-C	Iran	Serum concentrations	2007–2008	6	54	60	18–57	No association between vitamin B-12 deficiency and MS	Spearman and Pearson correlation
Saboor-Yaraghi et al., 2015 (53)	CT-C	Iran	—	nd	6	13	19	21–44	Vitamin A supplement upregulated gene expression in MS	Kolmogorov-Smirnov, Mann-Whitney, Wilcoxon

[1] ASA24, automated self-administered 24-h recall; BEBIS, Beslenme Bilgi Sistemi (Nutrition Information System); C, control group; CT, clinical trial; DHQ, Dietary Habits Questionnaire; EDSS, Expanded Disability Status Scale; HS-FFQ, high school FFQ; MS, multiple sclerosis; MSFC, Multiple Sclerosis Functional Composite; nd, no data; OT, observational trial; PDDS, Patient-Determined Disease Step; ref, reference; RRMS, relapsing-remitting multiple sclerosis.
[2] Mean age.

FAs

Seven of the reviewed articles assessed the effect of PUFAs on MS: 2 were observational studies, and 5 were clinical trials (Table 1 and **Table 2**). The intakes of SFAs and hydrogenated FAs from food must be controlled to avoid any increase in the MS inflammatory process (Table 1). A low-fat diet with antioxidant supplementation led to significantly lower C-reactive protein concentrations than did placebo. The oxidative stress and inflammatory markers 8-iso-prostaglandin F2α (8-iso-PGF2α) and IL-6 also decreased after dietary intervention, whereas catalase activity increased. These results suggest that diet and dietary supplements of long-chain omega-3 PUFAs, such as EPA and DHA, may modulate cell metabolism and MS-related inflammatory processes (26, 29).

A low-fat diet supplemented with ω-3 FAs decreased the rate of relapse and reduced fatigue (30) by ≤60% (24), generating significant improvements in the Expanded Disability Status Scale (EDSS) and also decreased the risk of developing the disease (28). This was also observed when the diet was enriched with vitamins A and E (27). The consumption of sources of long-chain PUFAs when exposure to sun is low can offer protection against the risk of MS: for example, the intakes of sesame seeds, hemp, and/or evening primrose oil, cod liver oil, or fish ≥3 times/wk during childhood and adolescence (25, 28).

Vitamin D

Of the 16 articles that reported on vitamin D, 11 were clinical trials and 5 were observational cohort studies (Table 1). Vitamin D concentrations may be influenced by bioavailability, metabolic and/or functional disorders, or even low sun exposure. A low vitamin D intake or low exposure to sunlight, its most important source, has been associated with a high risk of developing MS, as well as worsening of the disease and an increased risk of relapses (40). Indeed, the geographical distribution of the disease is usually associated with a reduced availability of vitamin D through low sun exposure. Serum concentrations of vitamin D were significantly lower in patients with MS than in healthy subjects. Vitamin D deficiency is considered to be a risk factor for MS (35, 38). The studies reviewed analyzed this risk by determining vitamin D serum concentrations or administering this vitamin to patients in order to observe any possible beneficial effects (Table 2).

Several studies, such as that by McDowell et al. (36), suggest that the contribution of this vitamin through diet is conditioned by the season of birth and sun exposure in childhood and adolescence. One study showed the protective effects of milk consumption. The risk of MS in offspring may decrease if pregnant women consume 2–3 glasses of milk/d (37), although a study by Munger et al. (39) concluded that the intake of whole milk, an important source of dietary vitamin D, was associated with an increased risk.

The influence of vitamin D amounts in the diet are associated with serious clinical disease activity (relapse, fatigue, disability) (36, 45), because concentrations were observed

TABLE 2 Dose and duration of clinical trials with PUFA and vitamin D administration[1]

Study, year (ref)	Dose	Duration	Effect
PUFAs			
Weinstock-Guttman et al., 2005 (30)	3.30 g ω-3 FAs/d	12 mo	Decrease in relapse rates and reduced fatigue
Shinto et al., 2009 (29)	4.8 g ω-3 FAs/d	3 mo	Immunomodulatory efficacy for regulating MMP-9 concentrations in MS
Mauritz et al., 2013 (26)	200 mg antioxidants/d in a low-fat diet	1.5 mo	Decreased oxidative stress, C-reactive protein, and other inflammatory markers
Pantzaris et al., 2013 (27)	19.5 mL PUFAs + γ-tocopherol/d	30 mo	Decreased annual relapse rate and disability progression
Rezapour-Firouzi et al., 2013 (28)	18–21 g PUFAs/d	6 mo	Decrease in proinflammatory (IL-17) and increase in anti-inflammatory cytokines
Vitamin D			
Wingerchuk et al., 2005 (46)	1000 IU/d	48 wk	Decrease in exacerbation rate; improvement in brain lesions (MRI)
Kimball et al., 2007 (33)	4000–40,000 IU/d	28 wk	Decreased number of brain lesions (MRI)
Smolders et al., 2010 (40)	20,000 IU/d	12 wk	Immunomodulatory efficacy in MS
Steffensen et al., 2011 (43)	2800 IU/d	96 wk	No prevention of bone loss in MS population
Dörr et al., 2012 (31)	200–10,200 IU/d	72 wk	Immunomodulatory efficacy in MS
Kampman et al., 2012 (32)	2800 IU/d	96 wk	No effect
Soilu-Hänninen et al., 2012 (42)	2800 IU/d	12 wk	Reduced new lesions and improved timed tandem walk
Toghianifar et al., 2015 (44)	7000 IU/d	12 wk	Improved inflammatory response

[1] MMP-9, matrix metalloproteinase 9; MS, multiple sclerosis; ref, reference.

to be lower in patients suffering relapses than during remission in 70% of MS cases (41). However, Langer-Gould et al. (34), in a study carried out during pregnancy and postchildbearing, showed that low vitamin D concentrations were not associated with an increased risk of postpartum MS relapses.

MS is a possible cause of secondary osteoporosis, and these is a consensus in the literature that vitamin D supplementation may be useful for the prevention and treatment of this disorder. When patients with MS received high doses of vitamin D as treatment for the illness (40), it was seen to play an important role in maintaining bone health by preserving calcium and phosphorus homeostasis (40, 44, 45).

The vitamin D doses used varied considerably between the different studies reviewed. The outcomes were a function of the intervention system: some of the studies analyzed increases in blood concentrations of vitamin D and found them to be correlated with relapses, fatigue, and EDSS score (31–33, 41, 42, 46); and some analyzed the MRI results in a search for new injuries or the progress of existing ones (31, 33, 41, 42, 46). Other articles looked at tolerance to the high vitamin D doses administered or the duration of the treatment, although neither hypercalcemia risk nor hypercalciuria was observed (33, 40).

Kampman et al. (32) showed the immunomodulatory effects of vitamin D combined with different forms of drugs, such as IFN-β, on processes related to disorders of oxidative and inflammatory metabolism. The oral administration of vitamin D acts through various mechanisms, such as anti-inflammatory and immunomodulatory mechanisms, in the inhibition of $CD4^+$ T cells that regulate the immune system (40). The re-establishment of optimal concentrations of vitamin D should be considered as part of MS clinical management because of its role in oxidative and anti-inflammatory metabolism (41, 45).

Other vitamins and antioxidants

Seven studies, all clinical trials, showed the influence of other vitamins and antioxidants (Table 1). The studies sought a direct association between blood concentrations of these vitamins and MS or significant differences between the dietary intake of foods rich in vitamins and their use as a supplement for the clinical treatment of the disease. Two articles referred to vitamin A (47, 53), 3 studies showed the effects of vitamin B-12 (50–52), and 1 studied the intake of vitamin-rich and antioxidant-rich foods (48). One article looked at the benefits of the coenzyme of α-lipoic acid for its cytokine profile and its use as an antioxidant (49).

Vitamin B-12 deficiency is associated with MS due to its role in the formation of the myelin sheath, in addition to its immunomodulatory effect (50). Several studies have shown that plasma concentrations of vitamin B-12 and folate decreased in patients with relapsing-remitting MS, but homocysteine concentrations increased significantly (20, 51). Other authors claimed that there was no correlation between vitamin B-12 deficiency and the timing of the onset and duration of MS symptoms and the disability types generated (52).

On the other hand, Bitarafan et al. (47) determined that treatment with vitamin A improved cognitive ability and countered disability in the upper extremity of the trunk, measured on the Multiple Sclerosis Functional Composite scale, but did not change the EDSS score, which measured neurological disability. Another study showed the effects of vitamin A on the gene expression of negative modulators of regulatory autoimmune T cells and suggested that vitamin A supplementation may represent a new approach for MS prevention and treatment (53).

A randomized, double-blind, controlled clinical trial conducted by Khalili et al. (49) suggested that lipoic acid

consumption by patients with MS improves total antioxidant capacity but does not affect other markers of oxidative stress. However, Hejazi et al. (48) did not detect significant differences between patients with MS and healthy controls in serum concentrations after the intake of antioxidant-rich foods (vitamins C and A and folate) and vitamin D.

Conclusions

MS therapy cannot be firmly associated with a particular diet due to the paucity of information on the effects of nutrition on this disease. Conclusions are sometimes limited due to the small number of subjects, and some studies used only a questionnaire on food intake. Even the EDSS test used in the majority of studies is not precise when determining disability and relapse rates.

Although there is no scientific evidence, to our knowledge, to recommend a specific diet, there is sufficient evidence to recommend the consumption of ≥1 food such as fish, low-fat foods, and whole grains, as well as the use of vitamins or ω-3 FAs as dietary supplements. A limited amount of data exists with regard to the beneficial effect of carotenoids and polyphenols from vegetables in patients with MS (1). Other bioactive molecules might have anti-inflammatory effects due to their antioxidant properties and activity against oxidative stress (49). However, there is sufficient evidence to state that vitamin D deficiency in serum is a risk factor for MS and therefore a potential biomarker of MS (36, 37). In addition, other studies showed a negative correlation between serum vitamin B-12 concentration and EDSS score. Vitamin B-12 has fundamental roles in central nervous system function, especially the methionine synthase–mediated conversion of homocysteine to methionine, which is essential for DNA and RNA synthesis. Therefore, vitamin B-12 deficiency can lead to an increased concentration of homocysteine. Further research is necessary to determine whether treatment with vitamin B-12 supplements delays disease progression.

Diets or alternative therapies cannot replace conventional treatment in patients with MS, but a healthy nutritional intervention is well accepted by patients with MS and may ameliorate their physical and inflammatory status. The findings that particular components of the diet can influence the degree of the inflammatory response suggest that an appropriate nutritive intervention may improve the course of MS and may be considered as a possible complementary treatment in the disease.

Future prospects in MS research should clarify the benefit (or lack thereof) of vitamin D intake from an early age to assess whether the vitamin is an immune- and disease-modulating compound that should be considered as part of MS clinical management. The relation between MS and vitamin A, folate, and vitamin B-12 in the formation of myelin should also be studied.

Acknowledgments

All authors read and approved the final manuscript.

References

1. Riccio P, Rossano R. Nutrition facts in multiple sclerosis. ASN Neuro 2015;7:1–20.
2. Yadav V, Bourdette D. Complementary and alternative medicine: is there a role in multiple sclerosis? Curr Neurol Neurosci Rep 2006;6: 259–67.
3. Ascherio A, Munger KL. Not too late to take vitamin D supplements. Ann Neurol 2014;76:321–2.
4. von Geldern G, Mowry EM. The influence of nutritional factors on the prognosis of multiple sclerosis. Nat Rev Neurol 2012;8:678–89.
5. Hadgkiss EJ, Jelinek GA, Weiland TJ, Pereira NG, Marck CH, van der Meer DM. 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.
6. Riccio P, Rossano R. [The role of nutrition in multiple sclerosis: a story yet to be written.] Revista Española de Esclerosis Múltiple 2013;5:24–37 (in Spanish).
7. Riccio P, Rossano R, Liuzzi GM. May diet and dietary supplements improve the wellness of multiple sclerosis patients? A molecular approach. Autoimmune Dis 2010 [cited 2015 Sep 30]. Available from: http://dx.doi.org/10.4061/2010/249842.
8. Schwarz S, Knorr C, Geiger H, Flachenecker P. Complementary and alternative medicine for multiple sclerosis. Mult Scler 2008;14:1113–9.
9. Leong EM, Semple SJ, Angley M, Siebert W, Petkov J, McKinnon RA. Complementary and alternative medicines and dietary interventions in multiple sclerosis: what is being used in South Australia and why? Complement Ther Med 2009;17:216–23.
10. Masullo L, Papas MA, Cotugna N, Baker S, Mahoney L, Trabulsi J. Complementary and alternative medicine use and nutrient intake among individuals with multiple sclerosis in the United States. J Community Health 2015;40:153–60.
11. Bagheri M, Maghsoudi Z, Fayazi S, Elahi N, Tabesh H, Majdinasab N. Several food items and multiple sclerosis: a case-control study in Ahvaz (Iran). Iran J Nurs Midwifery Res 2014;19:659–65.
12. Farez MF, Fiol MP, Gaitán MI, Quintana FJ, Correale J. Sodium intake is associated with increased disease activity in multiple sclerosis. J Neurol Neurosurg Psychiatry 2015;86:26–31.
13. Jahromi SR, Toghae M, Jahromi MJ, Aloosh M. Dietary pattern and risk of multiple sclerosis. Iran J Neurol 2012;11:47–53.
14. Massa J, O'Reilly EJ, Munger KL, Ascherio A. Caffeine and alcohol intakes have no association with risk of multiple sclerosis in a prospective study of women. Mult Scler 2013;19:53–8.
15. Mohammad-Shirazi M, Taleban FA, Ghafarpoor M. Macronutrients intake in Iranian multiple sclerosis patients. J Med Sci 2007;7:422–6.
16. Mähler A, Steiniger J, Bock M, Klug L, Parreidt N, Lorenz M, Zimmermann BF, Krannich A, Paul F, Boschmann M. Metabolic response to epigallocatechin-3-gallatein relapsing-remitting multiple sclerosis: a randomized clinical trial. Am J Clin Nutr 2015;101:487–95.
17. Nortvedt MW, Riise T, Maeland JG. Multiple sclerosis and lifestyle factors: the Hordaland Health Study. Neurol Sci 2005;26:334–9.
18. Ramsaransing GS, Mellema SA, De Keyser J. Dietary patterns in clinical subtypes of multiple sclerosis: an exploratory study. Nutr J 2009 [cited 2015 Sep 30]. Available from: https://www.ncbi.nlm.nih.gov/pubmed/19664270.
19. Rezapour-Firouzi S, Arefhosseini SR, Ebrahimi-Mamaghani M, Baradaran B, Sadeghihokmabad E, Torbati M, Mostafaei S, Chehreh M, Zamani F. Activity of liver enzymes in multiple sclerosis patients with hot-nature diet and co-supplemented hemp seed, evening primrose oils intervention. Complement Ther Med 2014;22:986–93.
20. Saka M, Saka M, Koseler E, Metin S, Bilen S, Aslanyavrusu M, Ak F, Kiziltan G. Nutritional status and anthropometric measurements of patients with multiple sclerosis. Saudi Med J 2012;33:160–6.
21. Salemi G, Gueli MC, Vitale F, Battaglieri F, Guglielmini E, Ragonese P, Trentacosti A, Massenti MF, Savettieri G, Bono A. Blood lipids, homocysteine, stress factors, and vitamins in clinically stable multiple sclerosis patients. Lipids Health Dis 2010 [cited 2015 Sep 30]. Available from: http://www.lipidworld.com/content/9/1/19.
22. Sorgun MH, Yucesan C, Tegin C. Is malnutrition a problem for multiple sclerosis patients? J Clin Neurosci 2014;21:1603–5.

23. Watson PE, McDonald BW. Seasonal variation of nutrient intake in pregnancy: effects on infant measures and possible influence on diseases related to season of birth. Eur J Clin Nutr 2007;61:1271–80.
24. Jelinek GA, Hadgkiss EJ, Weiland TJ, Pereira NG, Marck CH, van der Meer DM. Association of fish consumption and Ω 3 supplementation with quality of life, disability and disease activity in an international cohort of people with multiple sclerosis. Int J Neurosci 2013;123:792–800.
25. Kampman MT, Wilsgaard T, Mellgren SI. Outdoor activities and diet in childhood and adolescence relate to MS risk above the Arctic Circle. J Neurol 2007;254:471–7.
26. Mauritz E, Laliena A, Vallejo D, Tuñón MJ, Rodríguez-López JM, Rodríguez-Pérez R, García-Fernández MC. Effects of a low-fat diet with antioxidant supplementation on biochemical markers of multiple sclerosis long-term care residents. Nutr Hosp 2013;28:2229–35.
27. Pantzaris MC, Loukaides GN, Ntzani EE, Patrikios IS. A novel oral nutraceutical formula of omega-3 and omega-6 fatty acids with vitamins (PLP10) in relapsing remitting multiple sclerosis: a randomised, double-blind, placebo-controlled proof-of-concept clinical trial. BMJ Open 2013;3:e002170.
28. Rezapour-Firouzi S, Arefhosseini SR, Ebrahimi-Mamaghani M, Farhoudi M, Baradaran B, Ali TM, Zamani F. Erythrocyte membrane fatty acids in multiple sclerosis patients and hot-nature dietary intervention with co-supplemented hemp-seed and evening-primrose oils. Afr J Tradit Complement Altern Med 2013;10:519–27.
29. Shinto L, Marracci G, Baldauf-Wagner S, Strehlow A, Yadav V, Stuber L, Bourdette D. Omega-3 fatty acid supplementation decreases matrix metalloproteinase-9 production in relapsing-remitting multiple sclerosis. Prostaglandins Leukot Essent Fatty Acids 2009;80:131–6.
30. Weinstock-Guttman B, Baier M, Park Y, Feichter J, Lee-Kwen P, Gallagher E, Venkatraman J, Meksawan K, Deinehert S, Pendergast D, et al. Low fat dietary intervention with omega-3 fatty acid supplementation in multiple sclerosis patients. Prostaglandins Leukot Essent Fatty Acids 2005;73:397–404.
31. Dörr J, Ohlraun S, Skarabis H, Paul F. Efficacy of vitamin D supplementation in multiple sclerosis (EVIDIMS Trial): study protocol for a randomized controlled trial. Trials 2012 [cited 2015 Sep 30]. Available from: https://www.ncbi.nlm.nih.gov/pubmed/22316314.
32. Kampman MT, Steffensen LH, Mellgren SI, Jørgensen L. Effect of vitamin D3 supplementation on relapses, disease progression, and measures of function in persons with multiple sclerosis: exploratory outcomes from a double-blind randomised controlled trial. Mult Scler 2012;18:1144–51.
33. Kimball SM, Ursell MR, O'Connor P, Vieth R. Safety of vitamin D3 in adults with multiple sclerosis. Am J Clin Nutr 2007;86:645–51.
34. Langer-Gould A, Huang S, Van Den Eeden SK, Gupta R, Leimpeter AD, Albers KB, Horst R, Hollis B, Steinman L, Nelson LM. Vitamin D, pregnancy, breastfeeding, and postpartum multiple sclerosis relapses. Arch Neurol 2011;68:310–3.
35. Mazdeh M, Seifirad S, Kazemi N, Seifrabie MA, Dehghan A, Abbasi H. Comparison of vitamin D3 serum levels in new diagnosed patients with multiple sclerosis versus their healthy relatives. Acta Med Iran 2013;51:289–92.
36. McDowell TY, Amr S, Culpepper WJ, Langenberg P, Royal W, Bever C, Bradham DD. Sun exposure, vitamin D and age at disease onset in relapsing multiple sclerosis. Neuroepidemiology 2011;36:39–45.
37. Mirzaei F, Michels KB, Munger K, O'Reilly E, Chitnis T, Forman MR, Giovannucci E, Rosner B, Ascherio A. Gestational vitamin D and the risk of multiple sclerosis in offspring. Ann Neurol 2011;70:30–40.
38. Munger KL, Levin LI, Hollis BW, Howard NS, Ascherio A. Serum 25-hydroxyvitamin D levels and risk of multiple sclerosis. JAMA 2006;296:2832–8.
39. Munger KL, Chitnis T, Frazier AL, Giovannucci E, Spiegelman D, Ascherio A. Dietary intake of vitamin D during adolescence and risk of multiple sclerosis. J Neurol 2011;258:479–85.
40. Smolders J, Peelen E, Thewissen M, Cohen Tervaert JW, Menheere P, Hupperts R, Damoiseaux J. Safety and T cell modulating effects of high dose vitamin D3 supplementation in multiple sclerosis. PLoS One 2010;5:e15235.
41. Soilu-Hänninen M, Airas L, Mononen I, Heikkilä A, Viljanen M, Hänninen A. 25-Hydroxyvitamin D levels in serum at the onset of multiple sclerosis. Mult Scler 2005;11:266–71.
42. Soilu-Hänninen M, Aivo J, Lindström BM, Elovaara I, Sumelahti ML, Färkkilä M, Tienari P, Atula S, Sarasoja T, Herrala L, 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 Psychiatry 2012;83:565–71.
43. Steffensen LH, Jørgensen L, Straume B, Mellgren SI, Kampman MT. Can vitamin D supplementation prevent bone loss in persons with MS? A placebo-controlled trial. J Neurol 2011;258:1624–31.
44. Toghianifar N, Ashtari F, Zarkesh-Esfahani SH, Mansourian M. Effect of high dose vitamin D intake on interleukin-17 levels in multiple sclerosis: a randomized, double-blind, placebo-controlled clinical trial. J Neuroimmunol 2015;285:125–8.
45. van der Mei IA, Ponsonby AL, Dwyer T, Blizzard L, Taylor BV, Kilpatrick T, Butzkueven H, McMichael AJ. Vitamin D levels in people with multiple sclerosis and community controls in Tasmania, Australia. J Neurol 2007;254:581–90.
46. Wingerchuk DM, Lesaux J, Rice GP, Kremenchutzky M, Ebers GC. A pilot study of oral calcitriol (1,25-dihydroxyvitamin D3) for relapsing-remitting multiple sclerosis. J Neurol Neurosurg Psychiatry 2005;76:1294–6.
47. Bitarafan S, Saboor-Yaraghi A, Sahraian MA, Nafissi S, Togha M, Beladi Moghadam N, Roostaei T, Siassi F, Eshraghian MR, Ghanaati H, et al. Impact of vitamin a supplementation on disease progression in patients with multiple sclerosis. Arch Iran Med 2015;18:435–40.
48. Hejazi E, Amani R, SharafodinZadeh N, Cheraghian B. Comparison of antioxidant status and vitamin D levels between multiple sclerosis patients and healthy matched subjects. Mult Scler Int 2014 [cited 2015 Sep 30]. Available from: http://dx.doi.org/10.1155/2014/539854.
49. Khalili M, Azimi A, Izadi V, Eghtesadi S, Mirshafiey A, Sahraian MA, Motevalian A, Norouzi A, Sanoobar M, Eskandari G, et al. Does lipoic acid consumption affect the cytokine profile in multiple sclerosis patients: a double-blind, placebo-controlled, randomized clinical trial. Neuroimmunomodulation 2014;21:291–6.
50. Kocer B, Engur S, Ak F, Yilmaz M. Serum vitamin B12, folate, and homocysteine levels and their association with clinical and electrophysiological parameters in multiple sclerosis. J Clin Neurosci 2009;16:399–403.
51. Moghaddasi M, Mamarabadi M, Mohebi N, Razjouyan H, Aghaei M. Homocysteine, vitamin B12 and folate levels in Iranian patients with multiple sclerosis: a case control study. Clin Neurol Neurosurg 2013;115:1802–5.
52. Najafi MR, Shaygannajad V, Mirpourian M, Gholamrezaei A. Vitamin B12 deficiency and multiple sclerosis: is there any association? Int J Prev Med 2012;3:286–9.
53. Saboor-Yaraghi AA, Harirchian MH, Mohammadzadeh Honarvar N, Bitarafan S, Abdolahi M, Siassi F, Salehi E, Sahraian MA, Eshraghian MR, Roostaei T, et al. The effect of vitamin A supplementation on FoxP3 and TGF-β gene expression in avonex-treated multiple sclerosis patients. J Mol Neurosci 2015;56:608–12.