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## **Nutrition in multiple sclerosis**

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## **Abstract**

Multiple sclerosis (MS) is chronic idiopathic inflammatory demyelinating disease that causes neurological disability in young adults. Etiology of the disease is still unknown, but it has an immune-mediated basis and occurs in genetically susceptible individuals. Nutritional status and dietary habits in MS patients have not been extensively studied or reported, however individual findings suggest that many patients suffer from various forms of malnutrition. In patients with MS, malnutrition has been associated with impairment of the immune system; it affects mental function, respiratory muscle strength and increases a risk of specific nutrient deficiencies. These findings emphasize the need for nutritional support in MS patients. On the other hand, several nutritional compounds have been investigated as a possible treatment in MS, mostly polyunsaturated fatty acids and vitamin D, however their role in the treatment is yet to be confirmed. The aim of this review is to present data on the role of nutritional assessment and treatment in patients with MS.

## **Introduction**

MS is a chronic idiopathic inflammatory demyelinating disease that causes neurological disability in young adults, especially women, typically striking between 20 and 40 years of age (1). Etiology of the disease is still unknown, but it has an immune-mediated basis and occurs in genetically susceptible individuals.

Patients with MS suffer from different types of malnutrition which is often unrecognized causing fatigue and worsening the major symptoms. On the other hand, the majorities of MS patients use a different alternative therapy, which often includes special diets or dietary supplements in order to improve their health with hope to recover. However, this therapeutic approach has not been properly investigated (2,3).

The aim of this review is to present data on the role of nutritional assessment and treatment in patients with MS.

## **Diet as a cause of MS**

Dietary factors have repeatedly been suggested as a possible cause of MS, but without hard evidence (3). For instance, influence of fat consumption has been studied since almost 50 years ago (4). As a rational basis for the use of omega-3 and omega-6 fatty acids several pathophysiological mechanisms were proposed, which included immunomodulatory effect, effects on microcirculation and erythrocyte aggregation, antioxidant action, and also because of their structural significance to the CNS as components of the myelin membrane (3,5,6).

Population-based epidemiological studies suggested an association between the incidence of MS and the intake of saturated fat of animal origin; however findings were not confirmed by the majority of the case-control studies (7-11).

A large number of different diet compounds were also associated with MS (3), sweets (7), alcohol (9,12), smoked meat products (12), coffee and tea (10). However, none of the data were confirmed with subsequent studies.

Due to possible effect of human milk on the development of brain white matter (13), duration of breastfeeding was also investigated. Two retrospective studies investigated the role of breastfeeding on the incidence of MS, but results of the studies were not conclusive (14,15).

Risk factor which has been mostly associated with MS is vitamin D, even since epidemiological studies have found that MS prevalence increases from the equator to the poles (16,17). It has been published that disease activity also varies with sunlight exposure and low serum levels of 25-hydroxyvitamin D (18,19). The benefits from vitamin D could either be due to its beneficial effects on the nervous system or immune system regulation; there is data showing that vitamin D regulates myelin production by the oligodendrocytes as well as other neuronal processes (20). In particular, autoimmune diseases seem to be extremely sensitive to the availability of vitamin D (21). Until now, there is only one study which has directly analyzed the risk of MS based on the serum level of 25-hydroxyvitamin D before MS occurred (22). It was prospective, case-control study among more than 7 million US military personnel, from which they recognized 257 patients with MS. Results showed that among whites risk for MS significantly decreased with increasing levels of 25-hydroxyvitamin D (OR for a 50-nmol/L increase in 25-hydroxyvitamin D, 0.59; 95% CI 0.36-0.97). The inverse relation with multiple sclerosis risk was particularly strong for 25-hydroxyvitamin D levels measured before age 20 years. Among blacks and

Hispanics, who had lower 25-hydroxyvitamin D levels than whites, no significant associations between vitamin D and multiple sclerosis risk were found.

In people with MS and animal models of MS, products such as peroxynitrite and superoxide are formed that are highly toxic to neurons (23-25). Vitamins A, C, and E, may decrease free radical induced cellular injury and this is the rationale for their use in MS (1). However, until now we do not have evidence which support role of these vitamins in etiology of MS.

Diets high in gluten and milk are generally much more common in areas characterized by higher MS prevalence (26). An association between MS and food allergies has been hypothesized for a long time, but without clear scientific evidence of association. Recent study investigated whether or not cow's milk allergy (CMA) influences the subsequent risk to develop MS in a population-based cohort. Study showed that childhood CMA does not appear to be a risk factor for MS (27). The other association was gluten sensitivity and MS. It has been proposed that antigliadin antibodies have a role in MS and although some studies have found elevated levels of these antibodies, differences were not significant (28-30).

### **Nutritional status in patients with MS**

Malnutrition is a condition in which the body lacks sufficient nutrients to maintain healthy functioning and is due to improper or insufficient diet (31). In patients with MS malnutrition has been connected to impairment of the immune system, it affects mental function, respiratory muscle strength and increases a risk of specific nutrient deficiencies (32). Such impairments are clearly of clinical significance in MS as they contribute to existing symptoms, such as muscle wasting and weakness, fatigue and muscle spasms (4).

Nutritional status and dietary habits in MS patients have not been extensively studied or reported. Individual findings suggest that many patients suffer from various forms of malnutrition including weight loss, obesity or vitamin deficiency (3).

Weight loss and cachexia are often present in patients with MS (33-35). However, its incidence has not been determined and there is a paucity of information regarding its functional consequences to the MS patients (4). Naturally, proportion of malnutrition and weight loss increase with disability (37). Dysphagia, adynamia, and drugs potentially contribute to the development of undernutrition in patients with MS (31).

Of course, food intake is the one of most important contributors to malnutrition. The diet habits of patients with MS have not been properly investigated. Williams et al. examined 20 severely disabled patients with MS and found that energy intake as well as consumption of folic acid, iron, vitamin D and zinc is below recommended values (35). The other study, performed by Timmerman and Stuifbergen, analyzed the food intake of women with MS over three days and found that the patients consumed an inadequately small amount of carbohydrates, fibers, vitamin E, calcium and zinc (38). In contrast, their intake of saturated fat, protein, vitamin A and C, folic acid and iron was greater.

Weight gain and obesity have also been reported in MS (38,39). Hewson et al. showed high incidence of overweight in MS patients (40% in women and 44% in men) (39). In a recently performed cross-sectional study on the prevalence of obesity in veterans with MS (n=4703) slightly higher adjusted prevalence of overweight comparing to veterans in general was found (42.3% vs. 39.6%, respectively) but prevalence of obesity was lower (20.1% vs. 33.1%) (40). There are lots of factors contributing to overweight in patients with MS, including immobility



and subsequent low energy expenditure, steroids, anti-depressants, and an inactive daily life (3). On the other hand, obesity and an unhealthy eating pattern can aggravate fatigue syndromes, cause complications such as pressure sores or thrombosis, or may worsen disabilities already existing (3).

### **Nutritional assessment in MS**

In all patients with chronic illnesses evaluation of nutritional status is important. However, thorough and detailed nutritional assessment in every patient is neither practical nor essential for establishing accurate nutritional status. On the other hand, nutritional screening, if it is performed by trained personnel, could recognize patients who are at nutritional risk and need detailed nutritional assessment (41). For an overall picture of malnutrition a number of nutritional screening tools can be helpful, for instance the Subjective Global Assessment (SGA) (42), Mini Nutritional Assessment (MNA) (43), Malnutrition Universal Screening Tool (MUST) (44), and Nutritional Risk Screening 2002 (NRS 2002) (45). These screening tools combine number of questions with or without anthropometric measurements and helps to early identify patients at risk for malnutrition. Great number of hospitalized and chronically ill patients is malnourished, but despite this most physicians do not assess patient's nutritional status or ensure nutritional therapy (46).

Reports suggest that comprehensive nutritional assessment in patients with MS should be compounded of (31): evaluation of nutritional status, which includes medical history (dietary, medical, and medication), physical examination, anthropometric, body composition measurements and laboratory tests; calculation of nutritional and energy needs; evaluation of

potential dysphagia; scheduling nutritional intake; and planning for the eventual occurrence of complications.

Although not always a priority, it is important to obtain a thorough history before initiation of nutrition therapy. A comprehensive history and review of systems that uncovers impediments to deglutition and enteral absorption will identify a patient with impaired nutritional status (47).

Severe malnutrition can be easily detected by a physical examination, but mild to moderate malnutrition can be more challenging to identify. A careful clinical examination provides useful information to identify potential deficiencies. The examination includes assessment of patient's general condition which includes assessment of pallor, body fat stores, wasting of muscle mass, edema, skin rash, thinning of the hair, and evidence of specific nutrient deficit (48).

Anthropometric measurements need to be part of evaluation of every chronically ill patient. The measurement of anthropometrics is a convenient, inexpensive, noninvasive method for evaluating short-term and long-term nutritional status (49). The most common anthropometric measurement is body weight (50). Recent weight loss is a very sensitive marker of a patient's nutritional status and should be measured very frequently (51). Weight loss of more than 5% in 1 month or 10% in 6 months before hospitalization has been shown to be clinically significant (52). Other measurements include height, triceps skinfold, and midarm circumference. Upon anthropometric measures patients nutritional status can be evaluated, however, more optimal nutritional indicator is body mass index (BMI) which aims to overcome the limitations of changes in body weight and the need to compare it with expected normal values. Widely accepted definition of malnutrition is BMI of less than  $20 \text{ kg/m}^2$  and overweight as over  $25 \text{ kg/m}^2$  (53).

Composition measurements are used to determine total body mass, fat body mass and muscle mass. Body composition can be roughly estimated using combination of skinfold thickness and midarm circumference, but today, more sophisticated methods such as dual-energy X-ray absorptiometry, bio-electrical impedance analysis, computerized axial tomography and magnetic resonance imaging and whole-body counting/neutron activation are used (54).

Laboratory tests are useful in the evaluation of patients who are at risk for nutritional disorders, to confirm the nutritional assessment made by history and physical examination, to identify nutritional deficiencies before clinical findings are evident, and to monitor recovery from malnutrition (55). The most valuable studies in the assessment of nutritional status are the complete blood count (hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin, lymphocytes) and serum albumin or prealbumin concentration. Laboratory values must always be interpreted in light of the patient's history and physical examination.

#### Assessment of nutritional needs

Caloric need is determined by basal energy expenditure (BEE), level of physical activity, variations in food intake and illness state (50). There are multiple formulations used to determine a patient's caloric needs. The most commonly used formula is the Harris-Benedict (50) equation which combines weight, height and age. The daily recommended caloric intake is between 20 and 35 kcal/kg (actual weight) (31).

In patients who are well nourished and had relapsing remitting MS a "healthy diet" is recommended which is in concordance with current healthy eating recommendations (56). The

aim is to maximize plasma levels of essentially fatty acids, antioxidants, folate and vitamin B12 and maintain a healthy gut function (4).

As disability progresses, dietary intervention must be pointed to the individual needs. Typical symptoms that affect nutrient intake and nutritional status include: reduced mobility, fatigue, tremor, poor sight, dysphagia, cognitive difficulties, depression, pressure sores and the side-effects of drugs such as nausea, vomiting and diarrhea, dry mouth, weight gain and drug and nutrient interactions (4). Nutritional support in dysphagic patients requires a multidisciplinary approach, including a neurologist, nutritionist, dietician, speech and language therapist, and nurse, in order to perform a comprehensive evaluation as well as to develop a rehabilitation and education plan (31).

With or without dysphagia, if weight loss is progressive despite oral dietary intervention, the suitability of artificial nutrition should be considered. This may take the form of a naso-gastric feed as an interim measure, or a percutaneous gastrostomy (PEG) feeding regime (4). These can improve nutritional status, reduce risk of aspiration pneumonia and pressure sores and minimize the fatigue associated with feeding in MS (4).

### **Nutritional supplementation**

Many people with MS consider special diet as vital for improving their health status with aim to improve their sense of control over their disease (3,57).

Several studies investigated the role of polyunsaturated fatty acids in the treatment of MS.

Recently published Cochrane meta-analysis (1) analyzed six RCTs published between year 1973 and 2005 (58-62). Overall these studies account for 699 patients, 359 allocated to PUFA and 340

to oleic acid (control treatment). Results showed that omega-6 fatty acids had no benefit in relapsing remitting MS patients or in chronic progressive MS patients (RR=0.78, 95% CI 0.45-1.36; RR=1.67, 95% CI 0.75-3.72, respectively). Linoleic acid had no benefit in chronic progressive MS (RR=0.78, 95% CI 0.43-1.42). Slight decrease in relapse rate and relapse severity was associated with omega-6 fatty acids in some small studies, however these findings are limited by the limited validity of the endpoints. Omega-3 fatty acids had no benefit on progression in remitting or relapsing remitting MS patients. Authors concluded that the data available are insufficient to assess any potential benefit or harm from PUFA supplementation. A rationale for the therapeutic use of vitamin D in MS comes from animal studies in which the vitamin D was effective in preventing experimental autoimmune encephalomyelitis (63,64). Several studies investigated the role of vitamin D in treatment of MS. Goldberg et al. conducted an uncontrolled pre-post study in which patients with MS were treated with dietary supplements containing calcium, magnesium and vitamin D for a period of one to two years. Results showed that the number of exacerbations observed during the intervention was less than one half the number expected from case histories (65). Another uncontrolled study included 15 patients with relapsing-remitting MS who were treated with oral calcitriol for 48 weeks. The exacerbation rate (27%) was less than baseline. Brain MRI revealed enhancing lesions in five patients at baseline (33%) and in four (29%) at both 24 and 48 weeks. Authors concluded that oral calcitriol is safe and well tolerated for up to one year by diet compliant relapsing-remitting MS patients (66). Recently performed Cochrane analysis failed to include any of the published studies on the role of vitamin D in the treatment of MS and concluded that evidence bearing on the possible benefits and risks is lacking (1).

Because of its role in myelin formation and immunomodulatory effect, vitamin B12 was investigated as possible treatment for improvement of MS patients. RCT performed by Wade et al used combination therapy with lofepramine, L-phenylalanine, and intramuscular vitamin B-12 and showed that patients with MS improved after starting vitamin B-12 injections. The addition of lofepramine and L-phenylalanine added a further benefit. However, the effect of vitamin B12 could not be separated from other agents (67). An open label study used a massive dose of methyl vitamin B12 (60 mg every day for 6 months) in 6 patients with chronic progressive MS. Although the motor disability did not improve clinically, the abnormalities in both the visual and brainstem auditory evoked potentials improved more frequently during the therapy than in the pre-treatment period (68). Recently published Cochrane meta-analysis failed to include studies on the role of vitamin B12 in the treatment of MS (1).

## **Conclusion**

Diet has been investigated as a possible risk factor for MS during the last 5 decades; however studies were not able to confirm undoubtable association. In great number of patients with MS different type of malnutrition has been found including weight loss, cachexia and obesity. These findings emphasize the need for nutritional support in MS patients after nutritional status is assessed. Several nutritional compounds have been investigated as a possible treatment in MS, mostly polyunsaturated fatty acids and vitamin D, however their role in the treatment is yet to be confirmed. Future studies on this subject are needed.

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