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Review paper

MULTIPLE SCLEROSIS AND NUTRITION: A CONDENSED REVIEW

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Multiple sclerosis (MS) is a chronic, inflammatory, neurodegenerative demyelinating disease of the central nervous system (CNS).Inflammation is increased by hyper caloric Western-style diets, typically high in salt, animal fat, red meat, sugar-sweetened drinks, fried food, low in fibre, and lack of physical exercise. An anti-inflammatory dietary regimen, with or without administration of dietary supplements, thus supporting the general trend towards an amelioration of inflammatory status, should be considered.

Understanding the role of gut microbiota in health and disease can lay the foundation to treat chronic diseases by modifying the composition of gut microbiota through the choice of a correct lifestyle, including dietary habits and possibly probiotic supplementation.

Evidences from experimental, epidemiologic and clinical studies support the potential linkage between poor vitamin D status and the risk of developing MS, as well as, an adverse disease course. Correcting vitamin D status seems plausible in MS patients.

Keywords: Multiple sclerosis, diet, nutrition, vitamin D, anti-inflammatory diet

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Introduction

Multiple sclerosis (MS) is a chronic, inflammatory, neurodegenerative demyelinating disease of the central nervous system (CNS). While the aetiology of MS is not completely understood, it seems to be a multifactorial entity that is influenced by both genetic and epigenetic modifications [1].

At present, MS therapy is not associated to any particular diet, probably due to lack of information on the effects of nutrition on the disease [2]. However, diets and dietary supplements are frequently used by people with MS in the belief that they might improve disease outcomes and overcome the effectiveness limits of conventional treatments [3].

This review will focus on the interaction between diet and the immune system and inflammation. These effects can happen through direct manipulation of the inflammatory immune response and/or indirectly through modulation of the gut microbiota, which also manipulates the immune response. Where possible, clinical trials conducted on MS patients will be cited.

A. Interaction between diet and/or nutrients and the inflammatory response

Different kinds and amount of dietary factors can interact with enzymes, transcription factors, and nuclear receptors of human cells. This may induce specific modifications of cellular metabolism toward either catabolism or anabolism and modulate the inflammatory and autoimmune responses in our body [4]. Inflammation is increased by hyper caloric Western-style diets (Table 1), typically high in salt, animal fat, red meat, sugar-sweetened drinks, fried food, low in fibre, and lack of physical exercise. The persistence of this type of diet upregulates the metabolism of human cells toward biosynthetic pathways including those of proinflammatory molecules and also leads to a dysbiotic gut microbiota, alteration of intestinal immunity, and low-grade systemic inflammation [5, 6, 7].

On the other hand, exercise and low-energy diets based on the consumption of vegetables, fruit, legumes, fish, prebiotics, and probiotics act on nuclear receptors and enzymes that upregulate oxidative metabolism, downregulate the synthesis of proinflammatory molecules, and restore or maintain a healthy symbiotic gut microbiota. [2]

Dietary fat and fatty acids

The intake of certain types of fats has been linked to greater inflammation where omega-6 fats are pro-inflammatory and omega-3 fats are anti-inflammatory. Alpha linolenic acid (ALA; plant omega-3) converts to the anti-inflammatory precursors EPA and DHA, the omega-3 fatty acids we usually associate with fish oil [8, 9].

There have been clinical trials related to omega-3 supplementation and some evidence pointing to benefits for relapsing-remitting MS. In a systematic review Farinotti et al., 2012 concluded that omega- 3 PUFAs seem to have no major effect on the main clinical outcome in MS (disease progression), but they may tend to reduce the frequency of relapses over two years [3]. However, the data that are available are insufficient to assess a real benefit or harm from omega 3 PUFA supplementation because of their uncertain quality. In 2013, based on its anti-inflammatory and neuroprotective action, fish oil supplementation was found to be highly effective in reducing the levels of cytokines and nitric oxide in patients with relapsing-remitting MS (RRMS) under treatment with IFN-B2013 [10]. Dietary treatments with omega-3 fatty acids or a nutraceutical mixture of omega-3 and omega-6 fatty acids were found to improve patient wellness [11].

On this basis, in chronic inflammatory diseases such as MS, n-3 PUFA should prevail in the diet over the n-6 fatty acids. It is interesting to note that DHA is present in high concentrations in the brain and its levels decrease in patients with MS [2, 11].

Vitamin D

Epidemiological studies have highlighted possible links between vitamin D insufficiency and a wide range of human diseases. Reports have supported a role for 1,25 (OH)2D3 in mediating normal function of both the innate and adaptive immune systems. Crucially, these effects appear to be mediated via localized autocrine or paracrine synthesis of 1,25 (OH)2D3 from precursor 25-hydroxyvitamin D3 (25OHD3), the main circulating metabolite of vitamin D [12].

Accumulating evidences from experimental, epidemiologic and clinical studies support the potential linkage between poor vitamin D status and the risk of developing MS, as well as, an adverse disease course. However, the results of the trials on the clinical outcomes of vitamin D supplementation in MS patients are less consistent, which brought many

discrepancies in routine supplementation [13, 14]. Patients with MS have low levels of vitamin D [15], but this is true also for other chronic inflammatory diseases [16, 17]. Most association studies show approximately 10% reduction of magnetic resonance imaging (MRI) and relapse rate for each 10 nmol/l increment in the serum concentration of 25-hydroxyvitamin D (25(OH)D) [18].

Studies mostly assessed the mechanism of protective role of vitamin D in Experimental Autoimmune Encephalomyelitis (EAE). The proposed underlying mechanisms for this relationship are inducing inflammatory cells apoptosis [19], i.e. CD4+ T-cells [20], suppressing immune cell infiltration into the CNS, i.e. CD 11b + monocytes, decreasing Inducible Nitric Oxide Synthase [19, 20], as well as, inhibiting proinflammatory cytokine secretion including IL-12 and IFN-γ [21, 22].

Proposed management guidelines for Vitamin D and MS (Recommendations of an expert panel) [14, 18, 23]:

- Aim for a serum level of 25(OH)D of 40-50 ng/ml (100-125 nmol/l) in all MS patients who ask for advice.
- Supplementation seems to be reasonable for all MS and clinically isolated syndrome patients with serum 25(OH)D level below 40 ng/ml.
- Normality is currently between 30 and 100 ng/ml (75 and 250 nmol/l). Less than 10 ng/ml is considered as deficiency and a range between 11 and 30 ng/ml considered as insufficiency.
- In patients with vitamin D insufficiency or deficiency, a large replacing dose (e.g. 50,000 IU vitamin D per week for 8-12 week) is recommended.
- The serum vitamin D, and calcium level, as well as, patients' compliance should be checked after the initial phase of 8-12 weeks.
- A maintenance treatment of 1500-2000 IU daily or equivalent intermittent (weekly, biweekly or monthly) dose is recommended thereafter.
- A routine check of serum vitamin D level at least two times a year is recommended especially at the beginning of spring and autumn.
- Serum vitamin D evaluation for first degree relatives of MS patients at high risk age and supplementation in case of insufficiency (25(OH)D less than 40 ng/ml).
- Correction of vitamin D deficiency and insufficiency before pregnancy, as well as, a daily dose of 1500-2000 IU or equivalent biweekly intake in 2nd and 3rd trimesters; stopping supplementation if 25(OH)D serum level exceeds 100 ng/ml.

Vitamin A

Studies have shown that active vitamin A derivatives suppress the formation of pathogenic T cells in MS patients. Over the last 2 decades, it has become clear that vitamin A also has important roles in immune functioning, both in immunological tolerance and in adaptive immune responses. [25, 24] Recently Bitarafan et al., 2015 conducted a Randomized Placebo-Controlled Clinical Trial to investigate the effect of Vitamin A Supplementation (25000 IU/d retinyl palmitate for 6 month and 10000 IU/d for next 6 months) on the clinical status, relapse rate, and brain lesions. Vitamin A supplementation improved the multiple sclerosis functional composite score (measures the progression of disability as indicated by cognitive, lower and upper limb function), expanded disability status scale (determines lower limb function dominantly), relapse rate and brain lesions [26].

Lifestyle factors

Dietary factors and lifestyle may exacerbate or ameliorate MS symptoms by modulating the inflammatory status of the disease. It is argued that a nutritional intervention with anti-inflammatory food and dietary supplements can alleviate possible side effects of immune-modulatory drugs and the symptoms of chronic fatigue syndrome and thus favour patient wellness [2].

Recent studies shows that alcohol (beer, wine, or liquor) consumption is not associated to MS risk [27, 28]. Physical exercise influences the quality of life and may stimulate the production of anti-inflammatory cytokines [29].

B. Diet and the gut microbiome

The human gut carries, on average, about 540,000 microbial genes, representing the dominant microbes in this ecosystem. Approximately 55% of these genes constitute the core metagenome (i.e., genes shared among at least 50% of individuals), while many other genes appear to be unique and/or present in less than 20% of individuals [30]. The gut microbiota influences health and nutritional status via multiple mechanisms, and a mounting body of evidence recognizes that microbial metabolites have a major influence on host physiology. We are indeed meta organisms living with trillions (10^{14}) of microbial cells (roughly 10 times the cells of our body) and thousands of different microorganisms known as the gut microbiota. This complex ecosystem is an essential part of our organism and influences both our immune system and our metabolism. Therefore, it has a strong impact on our health [31].

The most common consequence of a dysbiotic gut microbiota is the alteration of the mucosal immune system and the rise of inflammatory, immune, metabolic, or degenerative diseases [32]. The composition of the intestinal microflora is highly individual and is influenced by many factors such as diet, physical activity, stress, medications, age, and so forth [33, 34, 35, 36].

Taken together, both disease promoting and ameliorating mechanisms can be induced by the gut microbiota, which interact closely and mutually with the host immune system. The nature of those interactions seems to depend on the composition of the gut microbiome and the immunologic state of the host. On these grounds, understanding the role of gut microbiota in health and disease can lay the foundation to treat chronic diseases by modifying the composition of gut microbiota through the choice of a correct lifestyle, including dietary habits. Whether enterotypes associated with long-term diets can be reversed by changes in the diet remains to be determined [37].

Probiotic Supplements and MS

Fleming et al., 2014 found that probiotic administration resulted in suitable trends in findings of MRI and few immunological determinations after 3 months in MS patients [38]. Recently Kouchaki et al., 2016 conducted a randomized double-blind placebo-controlled clinical trial to evaluate the effects of probiotic intake on disability, mental health and metabolic condition in subjects with MS [39]. The probiotic was containing *Lactobacillus acidophilus, Lactobacillus casei, Bifidobacterium bifidum* and *Lactobacillus fermentum* (each 2 _ 109 CFU/g). The study demonstrated that the use of probiotic capsule for 12 weeks among subjects with MS had favourable effects on expanded disability status scale (EDSS), parameters of mental health, inflammatory factors, markers of insulin resistance, HDL-, total-/HDL-cholesterol and malondialdehyde (MDA is a lipid peroxidation marker) levels

Highly selective experimental strategies will be needed to manipulate specific subsets or even single strains of bacteria as a therapeutic approach for MS. Rothhammer and Quintana 2016 [40], demonstrated that tryptophanase-positive bacteria, such as *Lactobacillus reuteri*, generate indole from dietary tryptophan, which is metabolized by the host to indole-3- sulfate (I3S), indole-3-propionic acid (I3PA) and indole-3-aldehyde (I3A). Indole, I3S, I3PA, and I3A cross the blood brain barrier and suppress pro-inflammatory activities by activating aryl hydrocarbon receptor (AHR) in astrocytes. Lack of dietary tryptophan or deficiency of AHR in astrocytes caused a failure to recover during chronic stages of EAE. MS patients seem to harbour deficits in the generation, uptake or stability of these anti-inflammatory metabolites, resulting in a decrease in their levels an in AHR-dependent immunoregulation [41, 40].

Another more drastic therapeutic approach aimed to restore gut eubiosis and downregulate inflammation may be represented by fecal microbiota transplantation [42].

C. Current Best Dietary advice for MS

Riccio et al. [46] showed that a healthy nutritional intervention is well accepted by people with multiple sclerosis and may ameliorate their physical and inflammatory status. A dietary regimen, mainly based on principles of Mediterranean diet, with or without administration of dietary supplements, determined an increase of the ratio n-3/n-6 PUFA serum concentration thus supporting the general trend towards an amelioration of inflammatory status. This was established in 12 out of 29 patients, on the basis of reduced active MMP-9 levels and of anthropometric parameters as well. Primary-Progressive MS patients were more responsive to the nutritional intervention with fish oil and lipoic acid [2]. Table 1 provides a summary of the role of diet and inflammation. The current recommendation for MS is a diet lower in saturated fats (fatty meat, fried food, confectionary, full cream dairy products) and high in monounsaturated fats (canola oil, olives and olive oil, nuts, seeds, avocados) and polyunsaturated fats (flaxseed oil, fish and fish oil) [2, 43, 44].

TABLE 1. SUMMARY: DIET AND INFLAMMATION

PRO-INFLAMMATORY DIETARY FACTORS	ANTI-INFLAMMATORY DIETARY FACTORS
Saturated fatty acids of animal origin [2].	Exercise and low-calorie diets based on the assumption of vegetables, fruit, legumes, fish, prebiotics, and probiotics [2].
Unsaturated fatty acids in the trans configuration (hydrogenated fatty acids) [47].	DHA and EPA found in seafood and fish oil [48].
Red meat [49, 51].	Pre and Probiotics [52].
Low vitamin D levels. It is now commonly accepted that vitamin D3 is also an immune-modulatory and anti-inflammatory agent, and it is ascertained that patients with MS and other chronic inflammatory diseases have a low level of vitamin D3 [53, 54].	Vitamins D and A, thiol compounds such as lipoic acid [55], and oligo elements such as selenium and magnesium [2, 53, 56, 57, 58].
Sweetened drinks, and in general hypercaloric diets rich in refined (low-fiber) carbohydrates, in addition to animal fat [2, 59, 60, 61].	All polyphenols, which are present in vegetables, cereals, legumes, spices, herbs, fruits, wine, fruit juices, tea, and coffee [62, 64, 63].
Increased dietary salt intake [65, 66].	n-3 Polyunsaturated fatty acids (PUFAs) [8, 9].
High body mass index: High body mass index (BMI) [67].	Resveratrol, a non-flavonoid polyphenol [68, 69].

Patients who do not eat oily fish at least three times a week can increase their intake of omega-3 fatty acids with supplements. Fish oil is the best source of EPA and DHA [45].

Patients who are overweight with a high compliance could be put on a low-energy diet (1,600-1,800 kcal) based on vegetables, whole cereals, legumes, fruit, and fish which may slow down the progression of the disease and ameliorate the wellness of MS patients, whereas hypercaloric diets with high intake of salt, saturated animal fat, fried food, and sugar-sweetened drinks may lead to the onset of postprandial inflammation and systemic low-grade inflammation. Diet should be integrated with prebiotics, probiotics, vitamins A and D, magnesium and selenium, and dietary supplements such as polyphenols, n-3 PUFA, and lipoic acid. Probiotics, such *as Lactococcus lactis, Bifidobacterium lactis, Clostridium butyricum, Lactobacillus acidophilus, Lactobacillus casei, Bifidobacterium bifidum* and *Lactobacillus fermentum*, can improve the intestinal microbial balance. Bowel functions and weight should always be under control [2, 46].

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