The molecular basis of nutritional intervention in multiple sclerosis: A narrative review

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\textbf{KEYWORDS}
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\textbf{Summary} It is commonly accepted that nutrition is one of the possible environmental factors involved in the pathogenesis of multiple sclerosis (MS), but its role as complementary MS treatment is unclear and largely disregarded. At present, MS therapy is not associated to a particular diet, probably due to lack of information on the effects of nutrition on the disease. To overcome the distrust of the usefulness of dietary control in MS and to encourage nutritional interventions in the course of the disease, it is necessary to assess the nature and the role of bioactive dietary molecules and their targets, and establish how a dietary control can influence cell metabolism and improve the wellness of MS patients.

The aim of this review is to provide a rationale for a nutritional intervention in MS by evaluating at the molecular level the effects of dietary molecules on the inflammatory and autoimmune processes involved in the disease. Present data reveal that healthy dietary molecules have a pleiotropic role and are able to change cell metabolism from anabolism to catabolism and down-regulate inflammation by interacting with enzymes, nuclear receptors and transcriptional factors. The control of gut dysbiosis and the combination of hypo-caloric, low-fat diets with specific vitamins, oligoelements and dietary integrators, including fish oil and polyphenols, may slow-down the progression of the disease and ameliorate the wellness of MS patients.

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\textbf{Abbreviations:} PPAR, peroxisome proliferator activated receptor; LXR, liver X receptor; RXR, retinoid X-receptor; NF-kB, nuclear transcription factor-kB; SREBP, steroid regulatory element-binding protein; ChREBP, carbohydrate responsive element-binding protein; SIRT-1/2, sirtuin-1/2, deacetylating enzyme; AMPK, AMP protein kinase; MMP, metalloproteinase; VEGF, vascular endothelial growth factor; TNF, tumor necrosis factor; ROS, reactive oxygen species; ICAM-1, intercellular adhesion molecule; VCAM-1, vascular adhesion molecule; n-3 PUFA, omega-3 polyunsaturated fatty acids.

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Introduction

Multiple sclerosis (MS) is a yet enigmatic, chronic, inflammatory and autoimmune disease of the central nervous system, characterized by blood brain barrier breakdown, perivascular inflammation, axonal and oligodendrocyte injury, and breakdown of the myelin sheath.\(^1\)\(^,\)\(^2\)\(^,\)\(^3\) Autoreactive T cells, macrophages and microglial cells,\(^4\) as well as antibodies and complement activation\(^5\) are involved in myelin degradation. MS is a complex and multi-factorial disease. Genetic predisposition, altered immune response and environmental (infectious and/or nutritional) factors are possible causative agents, but none of these factors alone can explain its origin.\(^6\)\(^,\)\(^7\)\(^,\)\(^8\)

Studies on the relationship between diet and MS are very few, and diets available to the MS patient are often lacking a scientific basis. At present, MS therapy is not associated to a particular diet. There is, however, an apparently great need to apply non-conventional therapies, and the majority of MS patients often use complementary or alternative treatments without informing the physician.\(^9\)\(^,\)\(^10\) The most intriguing aspects of MS are perhaps its uneven geographical distribution and the influence of migration in young age on disease course. According to the 2008 report of the World Health Organization (WHO) and the Multiple Sclerosis International Federation (MSIF), MS is prevalent in the more developed Western countries with high incomes (www.who.int/entity/mental_health/neurology/Atlas_MS_WEB).\(^11\)\(^,\)\(^12\) If the genetic background is not the discriminating element, and other environmental factors such as smoking or exposure to pesticides and heavy metals can be excluded, susceptibility to MS might be determined by the high-fat/high-carbohydrate and hyper-caloric "Western" diets rather than by microbial infections.

The aim of this review is to provide the molecular basis for the nutritional intervention in MS and to suggest why and how dietary molecules may represent a valuable tool to reinforce the effect of therapy and protect from relapses.

How nutrients influence cell metabolism and inflammation

To understand how diet can exacerbate or ameliorate MS symptoms, it is necessary to identify the dietary molecules, their targets and the molecular mechanisms involved in the control of the disease. Cells possess specific sensors to adapt themselves to changes in their environment, and changes in content and type of food molecules are the most common over time. Dietary molecules exert their direct influence on metabolism by modulating the expression and the activity of enzymes, hormones, transcription factors, and nuclear receptors.\(^13\)

The influence of dietary molecules and some common drugs on metabolism and inflammation is sketched in Fig. 1. The most important ligand activated nuclear receptors are the peroxisome proliferator-activated receptors (PPARs) [http://ppar.cas.psu.edu] and the liver X receptors (LXRs). Both are active as heterodimers with the retinoid X receptor isotypes \(\alpha, \beta, \gamma\) (RXRs), and are involved in the regulation of fatty acid metabolism. The PPAR isotypes \(\alpha, \beta/\delta, \gamma\), function as lipid sensors (in particular of oxidized fatty acids) and up-regulate the transcription of genes involved in fatty acid beta-oxidation in mitochondria and peroxisomes.\(^14\) LXRs are activated by the cholesterol derivatives oxysterols, and glucose. LXRs activate the sterol regulatory element binding protein-1c (SREBP-1c) and lipogenesis, but inhibit SREBP-2 and the synthesis of cholesterol.\(^15\)

The link between PPARs, LXRs and nutrients explain how cells respond to changes in nutritional status and regulate energy homeostasis. This link is also the molecular key to understanding how nutrients can influence the course of chronic inflammatory diseases. Besides their role as regula-
tors of energy homeostasis and metabolic diseases, PPAR and LXR isotypes have indeed an important role in the regulation of inflammatory and immunological pathways.

As shown in Fig. 1, oxidative metabolism is up-regulated by the AMP-activated protein kinase (AMPK) and PPAR pathways, which are activated by caloric restriction, physical exercise, and some bioactive molecules found in fruits, vegetables and fish. On the contrary, high intake of energy-rich nutrients leads to the up-regulation of anabolism, lipogenesis and cell growth, through the activation of the sterol regulatory element-binding proteins, SREBP-1c and SREBP-2, and the carbohydrate responsive element binding protein, ChREBP. It is important to note that lipogenesis is involved in the formation of new membranes, acylation, cell proliferation, inflammation and cancer.

In MS, the transcription factors involved in inflammation and autoimmunity — the activator protein (AP-1) and the nuclear transcription factor kB (NF-κB) — are activated and induce the expression of several pro-inflammatory genes and the production of pro-inflammatory molecules. The PPAR/RXR complex exerts a tight control over the expression of inflammatory genes by inhibiting NF-κB and AP-1, thus integrating metabolic and inflammatory signaling by inhibiting inflammatory gene expression. Thus, through their binding to PPARs — or directly by their binding to NF-κB and AP-1 — dietary molecules can inhibit the inflammatory process.

Dietary molecules to avoid in MS

The role of animal fat in MS

Among the dietary factors that have been considered most frequently for their deleterious influence on MS are saturated fatty acids of animal origin. In 1950, Swank suggested that the consumption of saturated animal fat is directly related to the frequency of MS, and in 2003 Swank and Goodwin reported that restriction of saturated fat induces remission of the disease. These effects were ascribed to the formation of large fat aggregates and obstruction of small capillaries. However, the influence of fat on cells is certainly more complex, since it is directed towards gene expression and cell growth and differentiation and is controlled at transcriptional level. Moreover, animal fats lead to the synthesis of cholesterol and decrease membrane fluidity, activate the CD14/TLR4 receptor complex, increase blood levels of C-reactive protein, and lead to the formation of TNF-α and to dysbacterial gut microbiota.

Gut and MS

The presence of IgA and IgG antibodies against gluten and gliadin observed in MS patients may indicate an increased gut permeability leading to cross-reactivity with self-
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**Figure 2** A simplified diagram illustrating the link between hypercaloric, high-fat, low-fibers diets and changes in gut microbiota profile. The resulting dysbiotic microbiota is able to extract more energy from the diet and increases lipogenesis and fat storage. As indicated, these metabolic changes lead to the breakdown of a correct crosstalk between gut and microbiota and promote, by different mechanisms, a moderate endotoxemia and a systemic inflammation that may trigger the exacerbation of MS symptoms.

proteins. The increased gut permeability may be ascribed to qualitative and quantitative changes of composition of gut microbiota induced by a high-fat/high carbohydrate diet. The purpose of these changes is to extract and store more energy from the diet while catabolic pathways are down-regulated. As shown in Fig. 2, the dysbiotic gut microbiota induced by a hypercaloric/high fat diet leads to a moderate metabolic endotoxemia and a systemic low-grade inflammation that may contribute to exacerbate MS symptoms.

In a dysbiotic microbiota, gut endotoxin/lipopolysaccharide (LPS) is increased, regulatory T cells (Treg) are defective, and the aryl hydrocarbon receptors and pro-inflammatory Th17 cells are activated. LPS leads to the dysfunction of the mucosal barrier and affects other tissues when its plasma level increases. Recent findings in EAE suggest that the proinflammatory condition resulting from the alteration of the gut bacterial population is linked to the development of autoimmune disorders, and in particular of MS. In this context, it has been reported that antibiotic treatment directed to alter gut microflora suppresses EAE.

**Cow milk and molecular mimicry in MS**

Environmental (microbial or dietary) factors can be associated with autoimmunity by molecular mimicry and epidemiological studies have shown that some proteins from cow’s milk could be responsible for the link between milk consumption and MS. Abnormal T cell immunity to several cow milk proteins was observed in MS patients and in children with autoimmune disease and CNS injury. However, the milk proteins that appear to be more detrimental in MS are the proteins of the milk fat globule membrane (MFGM proteins) and in particular butyrophilin (BTN). BTN is very similar to myelin oligodendrocyte glycoprotein (MOG), the MS candidate autoantigen, and induces experimental inflammatory responses in the CNS. MOG/BTN cross-reactive antibodies have been found in MS and anti-BTN/MFGM antibodies have been detected also in autism and coronary heart disease (CHD). On these grounds, we have suggested that the consumption of the MFGM proteins by MS patients should be discouraged.

**Dietary molecules to be preferred in MS**

**Bioactive natural compounds as complementary agents for the treatment of MS**

Specific dietary molecules might be able to counteract inflammation, autoimmunity, oxidative stress, and angiogenesis associated with MS, and for this reason they are considered as “healthy” molecules that can improve the wellness of MS patients. Among them, the most important are polyphenols and carotenoids from vegetables, omega-3 (n-3) long-chain polyunsaturated fatty acids (PUFA) from fish, and vitamins as vitamin D and niacin.
Polyphenols and carotenoids

Polyphenols are bioactive molecules found in vegetables, fruits, spices, herbs, soy, tea, wine and other fruit-based beverages. These dietary molecules are well known for their antioxidant activity, but recent findings indicate that they have additional neuroprotective properties, independent of their roles as antioxidants and radical scavengers. The rationale for the use of antioxidants in MS is based on the finding that oxidative stress, and in particular the generation of reactive oxygen species (ROS), are important components involved in inflammation and neuronal damage.

Polyphenols include well-known flavonoids (quercetin, catechins, genistein) and non-flavonoids (resveratrol, hydroxytyrosol and curcumin) molecules. Most polyphenols contain the catechol group, which has been recently associated with anti-inflammatory activity in stimulated microglia and neutrophils. Quercetin is found in onion, apple, citrus, and wine; resveratrol in red wine, chocolate, peanuts, berries, and black grapes; catechins in green tea; genistein and daidzein in soy; hydroxytyrosol in olive oil. Curcumin is a yellow phytochemical present in the spice turmeric (Curcuma longa) belonging to the ginger family. In general, polyphenols have antioxidant, antibacterial, antifungal, antiviral, anti-aging, anti-angiogenic, anti-carcinogenic, anti-proliferative and anti-inflammatory effects, and have been found to prevent neurodegenerative, cardiovascular, metabolic, autoimmune, and neoplastic diseases. They pass the blood brain barrier and, when consumed with pro-inflammatory meals, or in the course of microbial infection, may counterbalance their negative effects.

Polyunsaturated fatty acids from vegetables, seafood, and fish oil

Unsaturated vegetable oils are the alternative to saturated animal fat. Vegetable oils contain the essential fatty acids linoleic acid (n-6) e linolenic acid (n-3). The n-6 and n-3 fatty acids have opposing effects and their intake in the diet should be equivalent in healthy individuals. However, in Western diets, the n-6/n-3 ratio is largely increased and this causes a greater incidence of cardiovascular and inflammatory diseases. Indeed, linoleic acid leads to the production of the n-6 20:4, arachidonic acid (AA), which is the precursor of proinflammatory eicosanoids such as prostaglandins (2-series), leukotriens (4-series), and tromboxanes (2-series). Synthesis of these eicosanoids is favoured by insulin and inhibited by aspirin, but also by the n-3 long chain PUFA, i.e., 20:5 eicosapentaenoic acid (EPA) and 22:6 docosaexaenoic acid (DHA).

DHA is present at high concentration in the brain, but its levels decrease in MS patients. Both EPA and DHA are found in high proportion in oily fish and fish oil and show remarkable anti-inflammatory, antithrombotic and immunomodulating activities, which are comparable with statins. They also exert a number of neuroprotective effects and have a therapeutic value in several neurological diseases. The n-3 PUFA exert important effects on gene expression. They inhibit the transcription factors NF-kB, SREBP-1c, and LXR, and activate the nuclear receptor PPAR. As a consequence, n-3 PUFA decrease inflammatory processes and the synthesis of fatty acids, but increase fatty acid oxidation.

In LPS-activated rat microglial cells, fish oil inhibits the expression of MMP-9 in a similar way as IFN-β does. When inhibiting MAPK, DHA also increases the levels of tissue inhibitor of metalloproteinase-1 (TIMP-1). Like IFN-β, EPA and DHA inhibit the formation of IFN-γ, involved in myelin breakdown.

Few clinical trials indicate that n-3 PUFA may represent a good complementary treatment in the course of MS. Fish oil may be useful also in healthy conditions to improve motor performances.

Seed oils, from sunflower, corn, soybean, and sesame, contain more n-6 than n-3 fatty acids and their consumption should be limited in MS. Coconut oil has a high content of saturated fatty acids and is not indicated for MS patients. Olive oil is a good alternative to the oils reported above.

Hydrogenated fatty acids are found in margarine and in other treated fat, or are formed in frying. Differently from the natural ones, they are trans fatty acids (TFAs) and interfere with PUFA metabolism. The TFAs show pro-inflammatory effects and increase the levels of TNF-α, IL-6, and C-reactive protein. Their intake should be avoided or reduced.

Multiple dietary supplements

As indicated above, bioactive natural products act on several and different targets in the cell. On these grounds, it can be expected that an appropriate combination of some of them may result in a synergistic effect at low concentrations. A cocktail of polyphenols differing in antioxidant capacity and in the action on cellular targets can cover a large spectrum of activities, and can also protect n-3 PUFA from oxidation. The utility of multiple nutrient supplementation has been described in recent reports, but it is clear that, when possible, it is better to acquire the bioactive dietary components through a balanced diet.

Calorie restriction (CR)

Excessive calorie intake increases the risk by increasing the production of free radicals and levels of inflammation. A meal rich in refined carbohydrates may increase insulin levels, which in turn activate the enzyme 5-delta-desaturase (inhibited by EPA) and forms the n-6 pro-inflammatory arachidonic acid. Calorie restriction, obtained by decreasing food intake or by intermittent fasting, decreases the extent of oxidative damage, protects against diseases and is effective in slowing the progression of MS. Since the effects of calorie restriction are mimicked by RSV and other polyphenols, it can be expected that a combination of hypo-caloric, low-fat diets with polyphenols and other bioactive dietary supplements may improve the wellness of MS patients.
Physical exercise

In general, endurance exercise exerts beneficial effects on health by targeting the AMP-activated protein kinase AMPK and the AMPK-PPAR delta pathway. AMPK plays a key role in energy balance in the cell and leads to the suppression of ATP-consuming anabolic pathways as lipogenesis and the induction of ATP forming catabolic pathways as fatty acid oxidation. AMPK is a target of adipokines such as adiponectin and regulates food intake, body weight, and glucose and lipid homeostasis. Resveratrol can mimic and enhance the effects of training. Exercise training induces a decrease in plasma leptin levels and a reduction in gene expression of leptin receptors in the liver. The AMPK system appears to be down-regulated in EAE and AMPK agonists and metformin, a drug used to treat diabetes, attenuate the disease. In general, AMPK and PPAR-delta agonists are exercise mimetics. A combination of exercise with caloric restriction is effective in reducing inflammatory markers. As MS patients may be limited in mobility by their disease, they should practice only mild physical exercise and in the course of a rehabilitation program.

Vitamins, oligoelements and sulfur-containing antioxidants

The uneven geographical distribution of MS can be also ascribed to a lower availability of vitamin D and to a minor exposure to sunlight. It has been suggested that vitamin D could have an immunomodulatory role in the nervous system, and it certainly represents the most important vitamin for the treatment of autoimmune diseases and MS. Also, nicotinic acid and vitamin B12, vitamin E, and vitamin C should be taken into consideration. In particular, nicotinic acid activates the PPARs (indirectly) and the sirtuins (directly), stimulates the synthesis of prostaglandins 15d-PGJ2 and PGE2, raises HDL levels, corrects dyslipidemia, and in the form of nicotinamide protects the CNS from demyelination.

Oligoelements and other useful compounds with antioxidant activity that can be associated to the MS diet are: selenium, alpha-lipoic acid (ALA), N-acetylcysteine (NAC) and glutathione. ALA has immunomodulating effects, inhibits T cell migration, stimulates cAMP production, inhibits IFN-gamma synthesis, and is effective in the treatment of EAE. NAC, a precursor of reduced glutathione, is beneficial for antioxidant protection and energy metabolism. Finally, dietary magnesium could be beneficial, as its intake has been found to be inversely associated with inflammation.

Discussion

This review article addresses the issue of nutrition in multiple sclerosis. Nutritional intervention, that might represent a possible complementary therapy in MS in the future, is at present largely disregarded and dietary recommendations are usually not associated to conventional therapies. This might be ascribed to agnostic or skeptical positions towards the role of diet and dietary components in MS, because it is not yet clear how and why they might improve the course of MS. On this basis, the aim of this article is to provide a molecular basis for nutritional interventions in MS.

Statements of principal findings reported in this review article are based on careful, although not systematic, search of the literature and on our own experiments. Review criteria were based on the search of PubMed articles published on the different topics treated in the paragraphs, with particular regard to MS and other chronic inflammatory diseases. The abstracts and papers of retrieved citations were reviewed and prioritized by relevance of the content. References were further checked for additional material when appropriate.

The most important limitation for the evaluation of the impact of nutrition on the wellness of MS patients can be ascribed to the very limited number of clinical studies in this field. This is a bit like biting the tail, because the limited number of clinical evidences, the restricted types of dietary molecules used in clinical trials, or the limited number of patients enrolled in the studies, did not allow so far to achieve the scientific validity required for the approval of nutritional interventions in MS and this, on the other hand, make it difficult to perform other clinical studies.

However, as reported in this review, recent research data from in vivo and in vitro experiments appear to substantiate at molecular level a clear anti-inflammatory role of hypocaloric, low-fat diets and bioactive dietary supplements, and suggest that they might slow down the occurrence of relapses in relapsing-remitting MS. These evidences open new perspectives for further clinical trials based on the complementary treatment of chronic inflammatory diseases such as MS.

This review article introduces for the first time two important claims: (1) the link between diet, gut dysbiosis, inflammation and MS; (2) the molecular basis for the planning of nutritional interventions as complementary treatments of MS, based on combinations of both hypocaloric, low-fat diets and specific dietary supplements, including vitamins D, niacin, oligoelements, polyphenols and fish oil, together with sunshine and physical exercise.

With regard to the first point, gut dysfunction has been previously associated to MS only in three cases. Reichelt and Jensen suggested that MS might be associated to an increased gut permeability and to an increased uptake of large peptides from the gut, causing the formation of antibodies. Kidd suggested the involvement of gut dysfunction in MS, but only in terms of poor digestion and malabsorption. Ochoa-Repáraz et al. associated the gut dysbiosis observed in EAE to proinflammatory conditions and to the development of autoimmune diseases such as MS. In our paper, we suggest a link between nutritional styles, changes in the population of commensal microflora, increase of Th17 cells and LPS, gut permeability and production of low-grade inflammation that might contribute to MS relapses.

With regard to the second point, in this article we suggest that a combination of hypo-caloric low-fat diets with specific dietary supplements, in association with moderate physical activity and sunshine, might be much more effective than the administration of single dietary supplements, as it has been done in previous studies. Our suggestions are based upon hypotheses generated from our preliminary clinical studies, as well as from recent data reported in the literature showing that a low calorie low-fat diet activates...
enzymes capable to promote catabolic pathways and dump the synthesis of fat and pro-inflammatory molecules.

In particular, we suggest that a low-fat diet of around 1700 kcal/day, five times a day, based on the consumption of fish, multicolored vegetables and fruits, supplemented with prebiotics and probiotics, may represent a simple tool to prevent MS relapses or, at least, to improve the wellness of MS patients. The Mediterranean dietary pattern, with the addition of soy and black tea, may be effective as an anti-inflammatory diet.71 On the contrary, consumption of red meat, eggs, and animal fat (also including butter, fat cheese, and salami) should be avoided or limited, as should frequent consumption of fried foods, carbohydrates with high glycemic index [sugar and sweets]. The intake of water, green and black tea, coffee should be preferred to sweetened drinks. Consumption of reduced portions of pasta, rice and potatoes, chicken and turkey meats, ham, pizza, vegetables, legumes, fruits, fish, shellfish, crustaceans, mushrooms, and soy should be preferred. Consumption of skimmed milk and yogurt with prebiotics and probiotics instead of whole milk is recommended.

Such a diet provides healthy dietary molecules such as the polyphenols and n-3 PUFAs present in vegetables, fruit and fish. It has been actually shown that consumption of 200 mL of freshly squeezed orange juice per day is associated with a reduced risk of developing inflammatory arthritis.96

As shown in Fig. 1, the main targets of such dietary bioactive compounds are the PPAR nuclear receptors, sir-tuins and AMPK. The most important biological effects are the metabolic shift fromlipogenesis to lipolysis. Down-regulation of inflammatory processes through the direct or indirect inhibition of the transcription factors NF-kB and AP-1 is achieved as well.

The neuroprotective effects of polyphenols and n-3 PUFAs can be ascribed in particular to the activation of PPAR-gamma and inhibition of NF-kB. PPAR gamma activation has been found to be protective in MS models,97 while PPAR polymorphism has been associated with MS.98 PPAR-gamma agonists may promote remyelination by direct effects on oligodendrocytes,99 inhibit microglia activation, and decrease neuronal death.100 NF-kB polymorphisms differ in relapsing- remitting- and progressive-MS, and its inhibition is a key point in the control of the pathogenesis of autoimmunity and inflammation.101 However, the clinical use of PPAR-gamma agonists and NF-kB antagonists in MS remains poorly investigated.

On these grounds, the complementary treatment of MS patients with a hypo-caloric diet should be associated with physical exercise and sunshine and should be integrated with purified polyphenols (in particular resveratrol), fish oil, vitamins as vitamin D and niconitric acid, lipoic acid and oligoelements (in particular magnesium). The administration of dietary integrators should occur at least in the first three months and in the course of relapses. In this regard, while the dosage of fish oil supplementation does not represent a problem, decisions concerning the optimal dosage of polyphenols are far to be taken.

Diet polyphenols display a very low bioavailability.102 Their glycosides are hydrophilic and too large to enter the intestinal membrane, and the polyphenol aglycons released from gut microflora can be rapidly absorbed but have a poor solubility (around 20 μg/mL). Absorbed aglycons are then conjugated to glucuronides and sulfates in intestine and liver. On these grounds, it has been suggested that high intake of polyphenols may improve their bioavailability, due to saturation of intestinal formation of conjugates.103 On the other hand, data on the recommended daily allowances (RDAs) of purified polyphenols and the biological activity of their secondary metabolites are not yet available and it is not clear whether purified polyphenols should be taken alone or in combination and which is their optimal concentration or the best ratio. Another important limitation of purified polyphenols is their potential apoptotic effect on healthy cells.44 On these grounds, decisions concerning diet supplementation with purified polyphenols should be taken on the basis of preliminary clinical trials in addition to in vitro experiments and in vivo experiments.

Further in vitro experiments are needed to understand better the biological activities of dietary components and their secondary metabolites. In particular, polyphenolic compounds should be tested in cell cultures of neurons, astrocytes and microglial cells to determine their toxic concentrations. Moreover, the effects of bioactive dietary molecules on nuclear receptors, enzymes, and transcription factors should be evaluated at different concentrations and in different mixtures with other antioxidants, vitamins, and n-3 PUFAs. Results should be compared with those of already known pharmacological drugs, which are effective against inflammatory events and diseases other than MS. Of particular interest will be the studies with PPAR agonists and NF-kB antagonists.

However, the most important challenges in the future are represented by clinical studies. Clinical trials should be done by teams of neurologists, nutritionists, gastroenterologists and physiotherapists or exercise trainers to assess the impact of a nutritional intervention and exercise on the frequency of relapses and the wellness of patients. Nutritional intervention might be simply based on an appropriate diet. In the first few months of treatment, and in the course of relapses, dietary supplements might be added to the diet. Fish oil may be taken throughout the treatment time. The question may arise of how to make the selection of patients. Given that diet and dietary supplements are not drugs and do not substitute pharmacological therapies, patients should neither be selected on the basis of the different conventional treatment nor be kept out of drug treatment. Selection criteria might include for example: (a) young patients not yet under treatment, (b) patients with high serum levels of cholesterol and triglycerides, or (c) patients with symptoms of chronic fatigue syndrome. Assessment of serum levels of fibrinogen, TNF-α, IL-6, C-reactive protein, n-3 PUFAs, and specific polyphenols, as well as the determination of serum redox potential, should be performed if consumption of dietary supplements is planned.

Finally, as diet cannot be regarded as a pharmacological treatment and at the same time does not exclude conventional drugs, it is hoped that nutritional interventions in MS and other chronic inflammatory diseases will become more frequent in the clinical practice. After all, the biological effects of dietary components are now better understood at the molecular level, and a nutritional intervention under the control of nutritionists and gastroenterologists does not present particular risks.
The future of MS therapy is presently oriented only towards the development of more potent immunomodulatory and immunosuppressive drugs. Understanding the molecular mechanisms by which diet may influence the course of MS can now offer new perspectives for a complementary nutritional intervention in MS, and the development of new therapeutic agents that can open up the play against the disease.

Conflict of interest

The author has no conflict of interest with the context of this report.

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