The role of nutrition in multiple sclerosis: a story yet to be written

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ABSTRACT. The role of nutrition in multiple sclerosis (MS) is still unclear and MS therapy is not associated to a particular diet. In this review we show the molecular basis by which dietary factors and life style may exacerbate or ameliorate MS symptoms, by controlling both the metabolic and inflammatory pathways in the cell and the composition of gut microbiota. A persistent "Western style" diet may indeed lead to a dysbiotic gut microbiota, alteration of intestinal immunity and systemic inflammation. On these grounds, there are now good prospects for improving the well being of MS patients on the basis of nutritional intervention and healthy life style.
Key words: multiple sclerosis, inflammation, immunity, nutrition, gut microbiota.

RESUMEN. No está aún claro el papel de la nutrición en la esclerosis múltiple (EM) y todavía es incierto el papel de la dieta en el tratamiento de esta enfermedad. En esta revisión presentamos las bases moleculares por las cuales los factores dietéticos y los estilos de vida pueden exacerbar o mejorar los síntomas de la EM, controlando vías metabólicas e inflamatorias en la célula y en la composición de la microbiota. Un "estilo occidental" persistente de dieta puede, en verdad, dar lugar a una microbota intestinal disbiótica, alteraciones en la inmunidad intestinal e inflamación sistémica. Teniendo en cuenta estos fundamentos, existen en la actualidad excelentes posibilidades para mejorar el bienestar de los pacientes de EM, por medio de intervenciones en la nutrición y en los estilos de vida.
Palabras clave: esclerosis múltiple, inflamación, inmunidad, nutrición, microbiata intestinal.

Multiple sclerosis (MS) is a chronic, inflammatory and autoimmune disease of the Central Nervous System (CNS) in young adults[1]. The disease is characterized by perivascular inflammatory processes at the blood-brain barrier, degradation of the myelin sheath and relative impairment of the axons[2, 3]. The etiology of MS is unknown, and this may be ascribed to its multifactorial nature, i.e.: genetic predisposition, impaired immune response, and various environmental factors, such as infections by viruses or bacteria, heavy metal poisoning, smoking, or incorrect life style, including wrong dietary habits.

Although none of the above possible causes can explain alone the origin of the disease, the evidences for a possible influence of dietary habits on the disease are quite clear and are listed below[1-5].

1) The atlas of MS, presented in 2008 by the World Health Organization (WHO) in association with the International Federation of Multiple Sclerosis (MSIF), reports that MS is indeed a global disease but it is certainly more prevalent in Western countries with the highest income and most distant of the equator[4].

Moreover, in this context, studies on the influence of migration on MS support the idea that environmental factors can influence the course of MS, as they show that changing residence from an area of high incidence to another place with low incidence before age of 15 years, the low risk is acquired, while the migration after this age does not change the level of risk[5].

It is likely that the particular geographical distribution of MS and the influence of migration on the risk of disease are linked with nutritional, rather than with infectious or toxicological environmental factors. In the Western countries with high-income, where MS is more widespread, the lifestyle is indeed based on high-calorie diets, very rich in refined carbohydrates, protein and saturated fats of animal origin.

Another environmental factor related to diet and geographical distribution is the availability of vitamin D, which is lower at latitudes with lower exposure to sunlight.

Other clues that suggest a possible role of nutrition in the disease are as follows:

2) High fat/high carbohydrate diet is associated with postprandial inflammation[6-8];

3) High body mass index before age 20 is associated with 2x increased risk[9];

4) Dietary factors influence and direct cellular metabolism;

5) Diet and life style can modify the composition of gut microbiota and change the inflammatory state.

However, despite all, the role of nutrition in the

etiopathogenesis of MS is still unclear and remains to be proven.

Studies on the connection between nutrition and MS are very few[10-14] and, 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. However, the majority (about 70%) of patients with MS is looking for complementary and alternative treatments (CAM), and in particular is changing dietary habits, often without informing the physician[15, 16].

The aim of this review article 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 and to establish on a molecular basis whether a healthy diet can improve the wellness of MS patients.

❑ Diet, metabolism and inflammation

Usually, we consider food in terms of calories. However, the molecules of the diet are not simple substrates that provide energy to the cell: some of them can direct cellular metabolism towards either catabolism or anabolism (including the synthesis of pro-inflammatory molecules). This is not surprising: cells are integrated networks constantly responding to the environment (Figure 1). The ability to recognize changes in environmental conditions, and to adapt themselves to those changes, are essential for the viability of cells, and changes in quality and quantity of dietary molecules are the most frequent in the course of the day, even more than changes of chemical and physical parameters. The action of some dietary molecules is exerted through their binding to specific molecular targets in the cell: enzymes, nuclear receptors and transcription factors, which act as sensors capable of responding to changes in nutrients in the cellular environment[17]. It is important to note that cell sensors have a role not only in cell metabolism but also in the regulation of inflammatory processes and therefore they represent the molecular key to understanding how diet can influence the course of a chronic inflammatory disease[18, 19].

❑ The dietary "characters" of the story: compounds and elements that make the difference

Dietary factors that promote inflammatory processes

The components of the diet whose intake must be controlled to avoid the rise of inflammatory processes in MS, as well as in other chronic inflammatory diseases, are as follows (1-5):

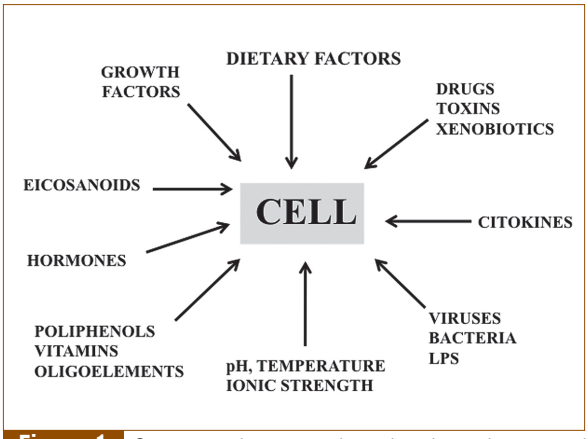

Figure 1 *Some environmental molecules, drugs and dietary factors that may influence cell activity.*

1) Saturated fatty acids of animal origin;

2) Cow's milk fats and proteins of the milk fat globule membrane (MFGM proteins);

3) Unsaturated fatty acids in the "*trans*" configuration (hydrogenated fatty acids);

4) Red meat;

5) Sweetened drinks, and in general hyper-caloric diets rich in refined (low-fiber) carbohydrates, in addition to animal fat.

1.- Fat of animal origin

Among the components of the diet taken into account more frequently for their deleterious influence on the course of MS, there are the saturated fatty acids of animal origin, which are found in foods such as whole milk, butter, cheese, meat, sausages, etc.

In 1950 Swank suggested that the consumption of saturated animal fat is directly correlated with the frequency of MS, but the link between restricted intake of animal fat and remission of MS was shown only in 2003[20].

In general, high fat diets induce lipogenesis, dysbiotic gut microbiota & inflammation.

In particular, saturated fatty acids can lead to (a-d):

a) Lipogenesis, formation of large fat aggregates and obstruction of small capillaries;

b) Synthesis of cholesterol and decrease of membrane fluidity;

c) Onset or increase of inflammation;

d) Increase of pathogenic bacteria of gut microbiota, more suited for fat utilization but with strong inflammatory influence.

More recent studies indicate that the action of saturated fat is controlled at the transcriptional level and influence both gene expression, cell metabolism, development and differentiation of cells. Finally, the intake of fatty acids of animal origin is often linked to a high calorie intake, which is on its own a detri-

mental factor. Moreover, as described later in this article, an excess of saturated animal fat leads to a dysbiotic intestinal microbiota, a possible cause of some human chronic disorders.

2.- Cow milk fat and the proteins of the milk fat globule membranes

Milk fat is dispersed in a homogeneous way and protected from oxidation thanks to a membrane made of particular proteins, called proteins of the milk fat globule membranes (MFGM)[21].

These proteins, which account for only 1% of milk proteins, have an informational rather than a nutritional value. In human lactation they are needed for the correct formation of the digestive, nervous and immune systems in infants. The importance of this flow of information is obviously lower in the case of cow's milk taken when the human body is ripe. In adult age, MFGM proteins of cow's milk no longer have an informational role and may be eliminated from the diet together with milk fat.

The removal of MFGM proteins from whole cow's milk is particularly relevant in the case of MS. The most representative MFGM protein (40% of total MFGM proteins), butyrophilin (BTN), is indeed suspected to have a role in MS, since it is very similar to MOG, the myelin oligodendrocyte glycoprotein, one of the candidate autoantigen in MS. BTN and MOG share the same behavior in MS experimental models and MOG/BTN cross-reactive antibodies have been found in MS, in autism and in coronary heart disease (CHD)[21].

On these grounds, the patient with MS should avoid the intake of whole cow milk and prefer skimmed milk, which, in addition, has no animal fat.

3.- Trans fatty acids

Trans fatty acids (TFAs) are unsaturated fatty acids that contain at least one non-conjugated double bond in the trans configuration[22]. As products of partial hydrogenation of vegetable oils, they were introduced in the 1960s to substitute animal fat, but only much later were found to have similar effects of saturated animal fat on metabolism. It is known now that TFAs interfere with the metabolism of natural unsaturated fatty acids, which have the "cis" configuration. They increase the levels of cholesterol and promote the formation of abdominal fat and weight gain.

TFAs are found in margarine and other treated vegetal fat, in meat and dietary products from ruminants, and in snacks, or may be formed in the frying. TFAs intake was found to be positively associated with markers of systemic inflammation in women[23]. Their intake should be avoided or reduced in MS.

4.- Red meat

Red meat contains more iron heme than white meat. The iron is easily nitrosylated and this facilitates the formation of endogenous nitroso-compounds (NOCs)[24]. Red meat intake shows indeed a dose –response relation with NOCs formation, whereas there is no such relation for white meat. NOCs are mutagenic: induce nitrosylation and DNA damage. Processed (nitrite-preserved red) meat increases the risk. Heterocyclic amines are formed during cooking of meat at high temperatures, but this is not specific for red meat[24]. Abnormal iron deposits have been found to be at the sites of inflammation in MS[25].

Consumption of red meat is associated with higher levels of γ-GT and hs-CRP[26].

Noteworthy, we do not have N-glycolylneuraminic acid (Neu5Gc), a major sialic acid, since an inactivating mutation in the CMAH gene eliminated its expression in humans. Metabolic incorporation of Neu5Gc from dietary sources - particularly red meat and milk products, can create problems, as humans have circulating anti-Neu5Gc antibodies and this implies the possible association with chronic inflammation[27].

Finally, meat contains arachidonic acid [the ω-6 (n-6) poly-unsaturated fatty acid, which is the precursor of pro-inflammatory eicosanoids (prostaglandins, thromboxanes, leukotrienes)].

5.- High intake of sugars and low intake of fibers

The intake of sweetened beverages and refined carbohydrates, with low fiber content, increases rapidly the number of calories and glucose level. The subsequent increase of insulin production promotes the production of arachidonic acid and its pro-inflammatory derivatives.

Natural bioactive compounds useful to prevent and tackle multiple sclerosis

Specific bioactive dietary molecules are able to counteract the effects of microbial agents and down-regulate the expression of inflammatory molecules. Among them, the most important compounds are the polyphenols and carotenoids from vegetables, n-3 polyunsaturated fatty acids (PUFA) from fish, vitamin D, thiol compounds as lipoic acid, and elements such as selenium, magnesium and zinc.

Most of the above compounds, with exception of PUFA, and selenium are known for their antioxidant properties. The rationale for the use of antioxidants in MS is based on the observation that oxidative stress is one of the most important components of the inflammatory process leading to degradation of myelin and axonal damage. However, recent studies indicate that dietary antioxidants have additional biological prop-

erties going far beyond the simple antioxidant activity, as they are able to counteract the negative effects of microbial agents and saturated or trans fatty acids, dumping the expression of pro-inflammatory molecules, oxidative stress and angiogenesis.

Polyphenols, which are present in vegetables, spices, herbs, fruits, wine and fruit juices, include flavonoids and non-flavonoids molecules[28, 29]. The most important flavonoids are quercetin (onions, apples, citrus fruit, wine), catechins (green tea), daidzein and genistein (soy).

The most important non flavonoids are resveratrol (chocolate, peanuts, berries, black grapes & red wine); curcumin (spice turmeric of ginger family, curry) and hydroxytyrosol (olive oil).

Among the carotenoids, the most important is lycopene (tomato, water melon, pink grape fruit).

Quercetin[30] is present mainly as glucoside, with a sugar bonded to one of the hydroxyl groups of the flavonol. Quercetin has anti-inflammatory, immunemodulatory and antiviral properties, reduces the proliferation of mononuclear cells of peripheral blood and decreases the production of IL-1β, TNF-α and MMP-9 (gelatinase B)[31]. Most of these effects are additive to those of interferon-β[32]. Quercetin passes the blood-brain barrier (BBB), inhibits phagocytosis of myelin by blocking the free radicals released by macrophages and also inhibits the expression of inflammatory cytokines.

In addition, quercetin inhibits angiogenesis, reduces the neutrophil-dependent inflammation, and has a neuroprotective effect as it improves Experimental Allergic Encephalitis (EAE), the animal model of MS. Quercetin is not toxic, but its oxidation product, quercetin quinone, is very reactive towards the-SH groups of proteins and glutathione, and may be toxic. The co-presence of lipoic acid or N-acetylcysteine should limit these toxic effects.

Resveratrol[33, 34] is glucuronate in the liver and absorbed in this form mainly in the duodenum. Only a limited number of molecules of resveratrol are absorbed as such. Resveratrol has a neuroprotective effect, reverses EAE, and shows anti-inflammatory and anti-carcinogenic properties. Its activity is similar to estrogens and protects the cardiovascular system. Depending on its concentration, resveratrol can induce the death of a wide variety of cells by necrosis or apoptosis. The resveratrol acts as a non-steroidal anti-inflammatory molecule and inhibits the production of numerous pro-inflammatory molecules, while stimulating catabolic pathways[35].

Curcumin[36] is the yellow dye present in the curry. It has strong anti-inflammatory properties. Catechins[37] are polyphenols present in green tea. They have anti-inflammmatory and anti-carcinogenic properties, inhibit the activity of metalloproteinases (MMP) and the intestinal absorption of lipids. Hydroxytyrosol[38], the main antioxidant of olive oil, is very effective against free radicals. Soy flavonoids, as daidzein and genistein, inhibit pro-inflammatory citokines and dump EAE[39].

It has been found that the anti-inflammatory effect of polyphenols *in vitro* may depend on their chemical structure[40]. Thus, a mixture of flavonoids and non flavonoids may be more effective than supplementation with only one polyphenol.

Lycopene is a carotenoid[41]. As antioxidant, it is much more powerful than beta-carotene and vitamin E.

Thiols and vitamins

Compounds containing thiol groups (-SH) as α-lipoic acid, glutathione and N-acetylcysteine must be taken into consideration as possible dietary supplements to be used for the complementary treatment of MS.

Lipoic acid[42, 43] (green plants and animal foods) has immunomodulatory anti-inflammatory properties, stimulates the production of cAMP and the activity of protein kinase A, inhibits the synthesis of interferon-γ and adhesion molecules, is effective in treating EAE, influence the migration of T cells in the CNS and stabilizes the integrity of the blood-brain barrier. Currently, studies are underway to determine the dosages to be used for the treatment of patients with multiple sclerosis. N-acetylcysteine passes through the BBB and protects from inflammation[44].

Other compounds and elements that may be used as supplements in MS are the vitamins D, E, C, B12[45], and niacin[46], melatonin, and elements such as zinc, selenium[47], and magnesium[48].

As already mentioned, the special geographical distribution of MS in the world can also be attributed to the reduced availability of vitamin D_3, due to insufficient exposure to sunlight in some countries, and the lack of vitamin D may be another possible cause of environmental origin of MS. At present, vitamin D represents the most promising molecule for the treatment of chronic inflammatory diseases such as MS[49, 50]. Direct interaction with genes and its immune-modulatory role may be the key to prevention of the disease by vitamin D.

Omega-3 (n-3) unsaturated fatty acids and poly-unsaturated fatty acids from vegetables, seafood and fish oil

n-3 unsaturated fatty acids and polyunsaturated fatty acids (PUFA) represent a valid alternative to saturated fatty acids of animal origin.

Vegetable and vegetable oils contain the essential fatty acids (EFAs) linoleic acid (n-6) and linolenic

acid (n-3). n-6 and n-3 fatty acids, have opposite effects and their presence in the diet should be equivalent[51]. However, in Western diets the ratio n-6/n-3 is increased from 6 to 15 times and this leads to a higher incidence of cardiovascular and inflammatory diseases. In fact, the linoleic acid leads to the formation of arachidonic acid (20:4), the precursor of the pro-inflammatory eicosanoids such as prostaglandins-2, leukotrienes-4, and thromboxanes-2. The synthesis of these eicosanoids is favored by insulin, and inhibited by aspirin, as well as by the n-3 long-chain PUFA EPA (eicosapentaenoic acid) and DHA (docosahexaenoic acid), which derive from n-3 linolenic acid.

Both DHA and EPA are found in seafood and fish oil. Both show remarkable anti-inflammatory, anti-thrombotic and immune-modulatory activities, comparable to those of statins[52, 53]. n-3 PUFA inhibit inflammatory processes and the synthesis of fatty acids and cholesterol, and instead they stimulate the oxidation of fatty acids. On this basis, in chronic inflammatory diseases such as MS, essential fatty acids (EFA) n-3 and n-3 PUFA in the diet should prevail 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.

Alike interferon-β, EPA and DHA inhibit the formation of interferon-γ, and fish oil inhibits in cultured microglial cells activated by LPS the expression of MMP-9 (gelatinase B), an important mediator of neuro-inflammation involved in myelin breakdown[54, 55].

Moreover, n-3 PUFA significantly decreased MMP-9 levels both in relapsing-remitting MS (RR-MS)[56], and in few clinical trials, indicating that n-3 PUFA may represent a good complementary treatment in the course of MS[57, 58]. Fish oil has been also found to improve motor performances in healthy rat pups[59].

Seeds oils, from sunflower, corn, soybean, and sesame, contain more n-6 fatty acids than n-3 fatty acids and therefore their assumption should be limited in MS, in order to limit the level of pro-inflammatory eicosanoid production. On the other hand, coconut oil has a high content of saturated fatty acids. Among vegetable oils, olive oil should be preferred for the good ratio between saturated and unsaturated fatty acids and because it contains the antioxidant hydroxytyrosol.

❑ How dietary factors influence cell metabolism and modulate inflammation: the molecular basis

At this point, the question arises of how dietary molecules (the above reported "characters" of this story) can exacerbate or ameliorate MS symptoms, and in general how they can favor or dump inflammation at molecular level. To this end, it is necessary to clarify what are their targets and the molecular mechanisms involved.

As mentioned above, cells possess specific sensors to adapt themselves to changes in their environment. Dietary molecules exert their influence on metabolism by modulating the expression and the activity of enzymes, hormones, transcription factors, and nuclear receptors[17].

The influence of dietary molecules and some common drugs on metabolism and inflammation is represented in the scheme of Figure 2.

The most important ligand activated nuclear receptors are the peroxisome proliferator-activated receptors (PPARs) [http://ppar.cas.psu.edu][60, 61] and the liver X receptors (LXRs)[62, 63]. Both are active only as heterodimers, i.e. if they are bound with the retinoid X receptor isotypes (RXRs)[64, 65]. Both are involved, but in a different way, in the regulation of fatty acid metabolism. PPAR isotypes up-regulate the transcription of genes involved in the beta-oxidation of fatty acid in mitochondria and peroxisomes. LXRs isotypes, which are activated by the cholesterol derivatives oxysterols, and glucose, have a relevant role in the synthesis of lipids. In particular, LXRs activate the sterol regulatory element binding protein-1c (SREBP-1c) and lipogenesis, but inhibit SREBP-2 and the synthesis of cholesterol.

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 regulators of energy homeostasis, PPAR and LXR isotypes are neuroprotective and have an important role in the regulation of inflammatory and immunological pathways[66-70], whereas RXR might be involved in myelin regeneration[71].

As shown on the left in Figure 2, oxidative metabolism is also up-regulated by the AMP-activated protein kinase (AMPK)[72] and the Sirtuins, a group of histone deacylating enzymes, which are activated by NAD^+ [73, 74]. Both form a network with PPAR pathways and are activated by calorie restriction, physical exercise, and some bioactive molecules (polyphenols and n-3 PUFA) found in fruits, vegetables and fish. On the contrary, as shown on the other side of an imaginary balance, 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.

In MS, the transcription factors involved in inflammation and autoimmunity – the activator pro-

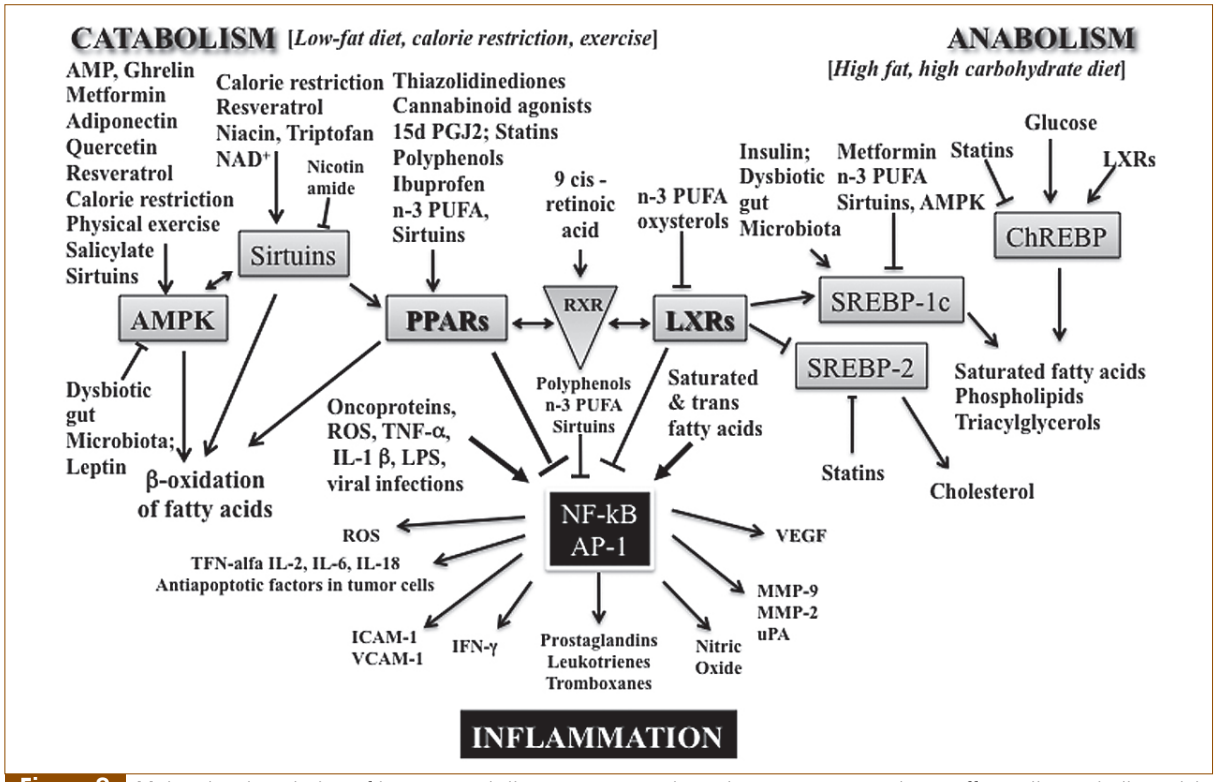

Figure 2 *Molecular description of how natural dietary compounds and some common drugs affectcell metabolic activity and inflammation through enzymes, nuclear receptors and transcription factors. PPAR: peroxisome proliferator activated receptor; LXR: liver X receptor; RXR: retinoid X-receptor; NF-kB: nuclear transcription factor-kB; SREBP: steroid regulatory element-binding protein; ChREBP: carbohydrate responsive element-binding protein; Sirtuins: SIRT-1/2, deacetylating enzymes; AMPK: AMP protein kinase; MMP: metalloproteinase; VEGF: vascular endothelial growth factor; ROS: reactive oxigen species; ICAM-1: intercellular adhesion molecule; VCAM-1: vascular cell adhesion molecule; n-3 PUFA: omega-3 polyunsaturated fatty acids.*

tein (AP-1) and the nuclear transcription factor kB (NF-kB) – are activated and induce the expression of several pro-inflammatory genes and the production of pro-inflammatory molecules[75]. The PPAR/RXR complex exerts a tight control over the expression of inflammatory genes by inhibiting NF-kB and AP-1, thus integrating metabolic and inflammatory signaling by inhibiting inflammatory gene expression. Thus, through their binding to PPARs, AMPK, and Sirtuins – or directly by their binding to NF-kB and AP-1 – some dietary molecules may inhibit the inflammatory process.

Calorie restriction

Diet is not only the intake of what is generically "good" or "bad" for our health. High calorie intake increases the production of free radicals and the degree of inflammation, and a meal rich in refined carbohydrates increases insulin level, that favors biosynthesis, including that of inflammatory molecules. Calorie restriction, obtained by decreasing food intake or by intermittent fasting ("one day and the other not"), decreases the extent of oxidative damage, dumps inflammatory processes and may be effective in slowing the progression of MS[76, 77]. The effects of calorie restriction are mimicked by resveratrol and other polyphenols.

Physical exercise

In general, physical exercise is very useful. At the molecular level, endurance exercise exerts its beneficial effect by acting on the protein kinase (AMPK) axis and involves the AMPK, Sirtuins and PPAR-δ network[78-80]. AMPK has a key role in energy balance: leads to suppression of the biosynthetic pathways, consuming ATP, and promotes catabolic pathways as the β-oxidation of fatty acids and the formation of ATP. Resveratrol and AMPK agonists such as metformin, a drug used in type 2 diabetes, can mimic or enhance the effect of physical activity and are effective in experimental encephalitis. Furthermore, physical exercise lowers plasma levels of leptin and reduces gene expression of leptin receptors in the liver[81]. The association of physical exercise with caloric restriction leads to a significant reduction of inflammatory markers[82]. MS patients

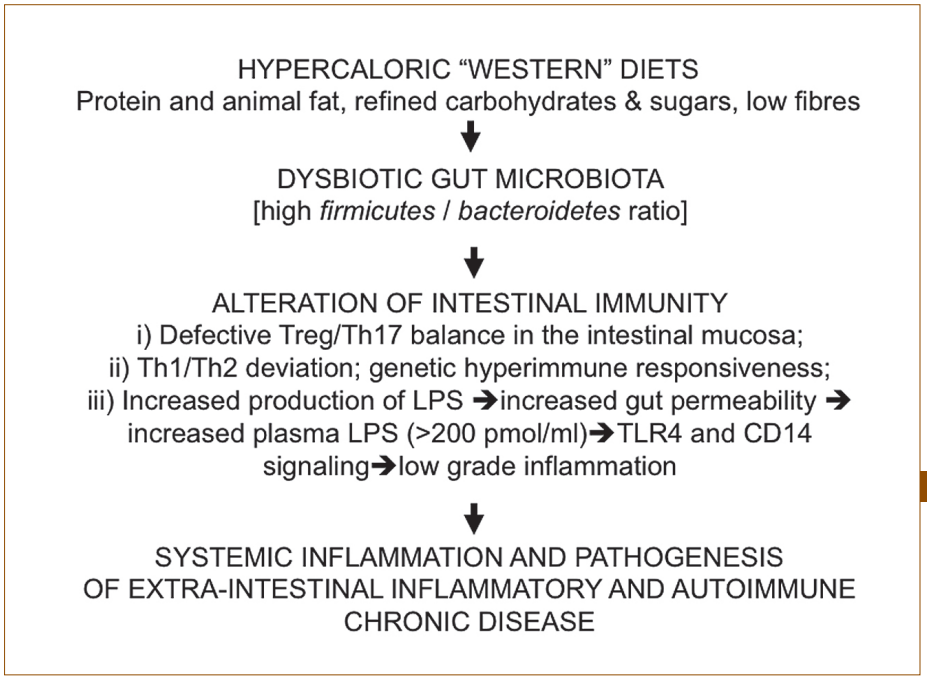

Figure 3 *Flow sheet of events from hyper-caloric "Western" diets to chronic diseases, through gut dysbiosis, intestinal immunity and systemic inflammation.*

should practice only mild physical exercise and in the course of a rehabilitation program.

The role of gut microbiota in MS

The presence of IgA and IgG antibodies against gluten and gliadin observed in some MS patients may indicate an increased gut permeability[83], probably to ascribe to qualitative and quantitative changes of the composition of gut microbiota, induced by a high-fat/high carbohydrate diet[84]. In the transition from a diet rich in carbohydrates but low in fat to a high-fat diet/high sugar diet, gut microbial population changes from the *Bacteroidetes* to *Firmicutes* and in particular to *Mollicutes*[84]. Overall, microbial diversity decreases. The result is a higher metabolic capacity suitable for Western-style diet to extract and store more energy from the diet, while catabolic pathways are down-regulated. The resulting dysbiotic gut microbiota leads to a moderate metabolic endotoxemia and a systemic low-grade inflammation that may contribute to exacerbate MS symptoms.

Actually, in the presence of 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[85-87] (Figure 3). LPS leads to the dysfunction of the mucosal barrier and affects other tissues when its plasma level increases above 200 pg/ml serum.

Recent findings in EAE suggest that the pro-inflammatory condition resulting from the alteration of the gut bacterial population is linked to the development of autoimmune disorders, and in particular of MS[88]. In this context, it has been reported that antibiotic treatment directed to alter gut microflora suppresses EAE[89].

The possible direct link between gut microbiota and MS has been shown recently by Berer *et al*.[90] in an experimental model of MS. They found that commensal microbiota may trigger autoimmune demyelination leading to relapsing remitting (RR) EAE, depending on the availability of the target autoantigen MOG.

If this would be the case, the discovery that the specific defect of the Treg/Th17 balance observed in MS models is also present in MS patients, could have important clinical implications, since this defect can be modulated by changes in the microbiota composition, which in turn is modulated by drastic dietary changes. Promoting Treg cell differentiation and reducing pathogenic Th17 cells might prevent recurrence of autoimmunity in MS patients.

A comparative study of De Filippo *et al*.[91] in children (1-6 years) from Florence and from Burkina Faso in Africa showed that long-term dietary habits have significant effects on human gut microbiota. The diet of the children from the rural village of Burkina Faso was based on the consumption of plant polysaccharides such as millet and sorghum (10 g fibers/day and 662-992 kcal/day), whereas the diet of Italian children was based on proteins, animal fat, sugar and refined carbohydrates (5,6 g fibers/day and 1068-1512 kcal/day). Analysis of fecal samples showed

the prevalence of the *Bacteroidetes* (73%), mainly *Prevotella* and *Xylanibacter*, and low levels of *Firmicutes* (12%) in the children from Africa. On the contrary, a prevalence of *Firmicutes* (51%) over the *Bacteroidetes* (27%) was observed in Italian children, but the *Bacteroidetes* shifted from *Prevotella* and *Xylanibacter* to *Bacteroides*. It is important to note that *Bacteroides* are selected among the *Bacteroidetes* because they can use also simple sugars in addition to complex glycans. Simple sugars are components of Western diet rich in protein, animal fat and sugars.

This study demonstrates that long-term dietary habits modify the population of gut microbiota: *Firmicutes* (as well as the parasitic *Mollicutes*) and the *Bacteroides* are associated with the consumption of a diet rich in proteins and fats of animal origin, whereas the *Bacteroidetes Prevotella* and *Xylanibacter* depend on the availability of a diet rich in complex carbohydrates and fiber fermentation. Firmicutes may be pathogenic as they may alter the intestinal immune system and may lead to endotossemia, systemic inflammation and chronic diseases. Conversely, feeding gut microbiota with a diet rich in fibers, or supplementing the diet with non-digestible food ingredients (prebiotics) and probiotics, stimulates the expansions of healthy microbiota that can tackle inflammation and chronic diseases and have therefore, a therapeutic effect.

❑ Concluding remarks

This review article deals with the role of nutrition in multiple sclerosis and other chronic inflammatory diseases.

The first aim of our study was to improve the well being of the patients with MS through a healthy targeted diet. The finding that particular components of the diet can influence the degree of inflammatory responses by acting on both cellular metabolism and composition of gut microbiota, unveiled that an appropriate nutritional intervention may ameliorate the course of the disease and may be therefore considered as a possible complementary treatment in MS. Conversely, since dietary habits may be detrimental and may promote a chronic state of inflammation, a wrong diet may be considered a possible contributory cause of MS, as for other chronic diseases.

Actually, in 2008 the World Health Organization (WHO) ascribed the causes of chronic diseases mainly to three risk factors: physical inactivity, unhealthy diets and tobacco use[92]. There are indeed some similarities of MS with other chronic inflammatory diseases, because all of them share some common inflammatory cytokine and signaling pathways. In particular, there are some evidences of a possible association of MS with inflammatory bowel disease (IBD), including vitamin D deficiency[93] and, in addition, MS appears with a greater frequency in patients with IBD[94]. As for MS, the prevalence of IBD is highest in Western industrialized countries and lowest in Asia and Africa.

Moreover, as shown in this paper (Figure 2), some drugs used to treat type II diabetes, such as the PPAR-γ agonists thiazolidinediones[95], and the AMPK agonist metformin have anti-inflammatory effects comparable with those of some dietary factors (polyphenols, omega-3-PUFA). For instance pioglitazone, a member of the class of thiazolidinediones, protects cortical neurons from inflammatory mediators, through the activation of PPAR-γ, nuclear receptors that prevent or attenuate neurodegeneration[96, 97].

This review clearly shows that catabolic and anabolic processes are competing with each other. In principle, as already described before, what promote the anabolism, can also promote the biosynthesis of pro-inflammatory molecules. To dump inflammation it is necessary to promote the catabolic rather than the anabolic pathways.

On these grounds, is no longer a question of what is in general healthy or detrimental. We can decide on a molecular basis what type of diet we have to choose for a nutritional intervention in MS, in order to attenuate inflammation and improve the wellness of MS patients. At the end, the goal of a nutritional intervention is the control of inflammation and this, as shown in this review, can be achieved mainly by controlling postprandial inflammation, the composition of gut microbiota and intestinal immunity.

A) Postprandial Inflammation

After each meal we may experience a transient and moderate oxidative stress and an inflammatory response depending on type and quantity of food. Dietary habits based on a persistent exposure to high fat/high refined carbohydrate meals stresses our immune/metabolic system and the subsequent possible failure of homeostasis may lead to immune and metabolic disorders of diverse nature. Taken together, the diet-dependent stress might be due to: 1) Calorie intake: the higher the calories, the more the oxidative stress induced; 2) Glycemic load of a meal: acute postprandial glycemic peaks induce a release of insulin much higher than that required; 3) Lipid pattern: animal fat, trans fatty acids and n-6 PUFA promote postprandial inflammation, whereas n-3 PUFA and polyphenols suppress postprandial inflammation; 4) Calorie restriction, physical exercise and polyphenols attenuate the level of metabolic inflammation.

B) Gut microbiota and the impact of diet on its composition[87, 91, 98-101]

We are meta-organisms resulting from a millenary co-evolution with a very large number (about 100 trillion) of microbial cells (anaerobic and aerobic bacteria, virus, yeast) living in our organisms: the gut microbiota. Gut microbiota provides a number of metabolic functions, which we have lost in the course of times, protects against enteropathogens, and contributes to normal immune functions. Although there is a wide choice between thousand of different bacterial populations, two dominant bacterial divisions - the *Bacteroidetes* and the *Firmicutes* - account for about 90% of the total. This observation may be useful to simplify the discussion concerning the role of gut microbiota in chronic inflammatory diseases. It is now becoming increasingly clear that it is possible to change the ratio *Bacteroidetes* / *Firmicutes* (B/F) by long-term dietary habits. The B/F ratio increases in association with a diet rich in complex carbohydrates (non digestibile by our enzymes) because the symbiotic and usually non harmful *Bacteroidetes*, such as *Prevotella* and *Xylani bacter*, love to have complex glycans to eat. Conversely, a diet rich in protein, animal fat, sugars and refined carbohydrates change the gut microbiota profile and increase the population of *Firmicutes* (including the *Mollicutes*), more suited to extract and harverst energy from Western diets, but often pathogenic. The consequent microbial imbalance and the decrease of gut microbiota biodiversity, called dysbiosis, leads to the disruption of the complex interplay between the microbiota and its host, and contribute to chronic inflammation and to pathological conditions, such as obesity, cardiovascular disease and metabolic syndromes such as insulin resistance and type 2 diabetes, including the risk of immune mediated diseases.

On these grounds, understanding the role of gut microbiota in health and disease can lay the foundation to treat chronic diseases by modify the composition of gut microbiota through the choice of a correct life style including dietary habits.

Nutritional Intervention in MS: The choice of diet and dietary supplements

In this review article, we suggest that intestinal dysbiosis may represent a link to inflammation and to exacerbations in multiple sclerosis.

If we make the assumption that this is true and that the course of MS may be influenced by the status of gut microbiota - as in the case of other chronic inflammatory diseases - then we may have to modify a dysbiotic gut microbiota by a long-term dietary intervention, with a hypo-caloric diet, prebiotics, probiotics and dietary supplements.

Present data reveal that healthy dietary molecules (mostly antioxidants) have a pleiotropic role, since they are able to direct cell metabolism towards catabolism and down-regulate anabolism and inflammation by interacting with specific enzymes and transcriptional factors.

On these grounds, the control of gut dysbiosis and the combination of low calorie, low-fat diets with specific vitamins, oligoelements and dietary supplements, may slow-down the progression of the disease and ameliorate the wellness of MS patients.

Dietary supplements should include omega-3 PUFA, lipoic acid, vitamin D and other vitamins, in particular niacin, and polyphenols. Dietary supplements, with the only exception of omega-3 PUFA, which are normal constituents of our body, are useful at the beginning of the nutritional intervention but their use should be restricted to only a limited period of time.

This is particularly valid in the case of polyphenols. They are found in plants in the form of glycosides, esters or polymers, too large to enter the intestinal membrane. Aglycons released from gut microbiota are conjugated to glucuronides and sulfates in intestine and liver. Their solubility and bioavailability are very poor (μM)[102]. Polyphenols are not well known molecules with regard to their biological effects and special precautions should be used when supplementing the diet with them. On one hand, they can down-regulate the synthesis of pro-inflammatory molecules in the course of inflammatory processes, on the other hand, they can stimulate cell activity in resting cells, but a persistent stimulation can induce the apoptosis of healthy cells. Furthermore, it should be taken into account that polyphenols may inhibit the human cytochrome P450 enzymes involved in drug metabolism and this could lead to undesirable therapeutic consequences[103]. These considerations suggest that supplementation with purified polyphenols should be taken on the basis of preliminary clinical trials to test their effectiveness as complementary therapeutics.

Future prospects

Clearly, we are only just beginning to understand the nature of the interactions of gut microbiota with the host's immune system especially in the context of autoimmune diseases at sites distal to the intestine and much work remains in terms of understanding the role of gut inflammation in MS.

In the future, clinical trials have to address the influence of diet and dietary supplements on CNS autoimmunity. To answer to the question as to whether gut microbiota has a role in the course

of MS, it is necessary: 1) to assess gut microbiota composition; 2) to evaluate defects in intestinal immune system; 3) to define personalized diets and exercises. Future research should regard also the study of PPAR-gamma agonists and NF-kB inhibitors with particular attention to their anti-inflammatory and neuroprotective actions. Clinical supplementation with polyphenols should performed also during pharmacologic therapy.

In any case, education about protective dietary constituents should be embraced by clinicians. For instance, encouraging patients to include fiber or complex carbohydrates in their diet, supplementing with probiotics, choosing "healthy" n−3 fats over pro-inflammatory n−6 fats, and limiting meat consumption, may optimize the well being of MS patients[13, 14].

Overall, anti-inflammatory conventional therapies have been almost successful, however drugs that can protect and favor repair mechanisms are still missing. Once we have accepted that the causes of chronic inflammatory diseases are represented also by a wrong life style, we can decide to help people stay healthy by providing nutritional guidance and physical activity opportunities already in childhood. For the moment, there are only good prospects for improving the well being of patients with MS. We are only at the beginning of the story.

Conflict of interest

The authors declare no conflicts of interest within the context of this work.

Acknowledgements

Funding by the Italian Foundation for Multiple Sclerosis (FISM), Grant 2007/R/15 for the Project "Healthy and Functional Foods for MS patients", and 2010/R/35 for the Project "The Molecular Basis for Nutritional Intervention in Multiple Sclerosis" is acknowledged.

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