Dietetic Habits in Multiple Sclerosis

Subjects: Neurosciences

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Multiple sclerosis (MS) is a disabling immune-mediated demyelinating neurodegenerative disease with an estimated prevalence of 1 in 1000 in populations of European descent. It primarily affects females (F:M = 2–3:1) mainly between the ages of 15 and 55 years.

multiple sclerosis | pediatric-onset multiple sclerosis | nutrition | diet | gut microbiota | gut-brain axis | blood-brain barrier | vitamin D

1. The Gut-Brain Axis in Multiple Sclerosis

The multiple sclerosis (MS) gut-brain axis (GBA) contemplates a dysbiosis-induced pro-inflammatory gut environment responsible for a leaky gut [1] allowing the emergence of activated myelin-specific bystander T cells which regulate the cytokine milieu in the central nervous system (CNS) and the function of neurons and glial cells [2]. Clinical [relapsing-remitting (RR) course with subsequent progressive disability] and pathological similarities between MS and the murine model of experimental autoimmune encephalomyelitis (EAE) allow the latter to be considered as a suitable model for the study of MS. Through this model, studies have confirmed that high-fat diets, especially if high in saturated fats, are relevant MS triggers [3][4]. Obesity itself, due to the adipose tissue's inflammatory properties mediated by adipokines production (e.g., adiponectin), has been suggested to contribute to the pro-inflammatory status of MS, which also has impacts on the quiescence of CNS-resident microglia [5][6].

1.1. The Intestinal Barrier

The intestinal barrier is a complex functional unit composed of mucosal and luminal elements (i.e., epithelial cells layer; mucosal barrier; innate and acquired immune components); neuroenteric, vascular, and endocrine systems; digestive enzymes; and gut microbiota (GM). This barrier plays a key role in protecting against enteric organisms, their toxins, and bio-products associated with the health and disease susceptibility of organs/systems [7][8]. The recently discovered gut-vascular barrier controls the translocation of gut bacteria and antigens into the bloodstream [9][10].

The gut-(liver)-brain axis connects the GM, neuroendocrine and neuroimmune systems, autonomic nervous system, and enteric nervous system with the CNS [2][11]. The GM consists of trillions of commensal microorganisms that maintain the integrity of the mucosal barrier and contribute to normal host physiology [7]. Factors such as an

unbalanced diet, infections, antibiotics, stress, and environmental factors can lead to dysbiosis and increased intestinal permeability [12][13][14]. Dysbiosis is associated with various diseases, including gastrointestinal and systemic inflammatory diseases [15].

GM dysbiosis can also impact the onset and progression of neurological disorders such as MS by affecting metabolic pathways and interacting with host immunity [16][17][18][19][20].

Identifying a characteristic/diagnostic composition of microbial communities associated with the gut microbiota of MS patients is challenging due to variations between studies and individual profiles [19][20]. However, reduced microbial diversity is commonly observed, which is characterized by an increased Firmicutes/Bacteroides ratio and prevalence of species producing endogenous ethanol, lipopolysaccharide, and reactive oxygen species [21][22].

These biochemical factors, along with pro-inflammatory T-helper types and cytokine patterns, contribute to intestinal inflammation and impairment of the barrier function (leaky gut) [17][23].

In an MS mouse model, Streptococcus thermophilus ST285 has been observed to switch cytokine responses to myelin peptides from pro-inflammatory to anti-inflammatory patterns [24]. The significance of increased abundance of Akkermansia species in MS patients and the EAE mouse model is still debated, with suggestions of a compensatory effect rather than a direct association with EAE progression and MS pathogenesis [25][26].

Considering differences in patient selection methods, environmental factors, and dietary habits, certain species (e.g., Faecalibacterium, Eubacterium rectale, Corynebacterium, Fusobacteria, Bacteroides stercoris, and Bacteroides coprocola) [17][27] are generally reduced in MS patients compared to healthy controls in some studies. These species are responsible for decreased production of metabolites such as bacterial lipid 654, a Toll-like receptor 2 ligand derived from gastrointestinal and oral bacteria [28][29][30], and short-chain fatty acids (SCFAs) such as butyrate and propionic acid [1][31][32].

SCFAs, produced by the colonic fermentation of dietary fibers and resistant starch, are speculated to play a key role in neuro-immunoendocrine regulation [33]. A secondary increase in species related to oxidative levels is observed in progressive MS or more severe disease forms [34][35][36], and it is sufficient to induce EAE sensitivity [37][38]. Saturated fatty acids (FAs) have a close relationship with autoimmunity phenomena in MS, as their concentration and composition regulate immune cell polarization, differentiation, and function, with a protective role in blood-brain barrier function. They are critical players in CNS chronic inflammation, progressive degeneration, and remyelination [22][39].

Additionally, a negative association with polysaccharide-digesting bacteria such as B. thetaiotaomicron is often observed [40].

1.2. The Blood-Brain Barrier

The BBB plays a crucial role in maintaining the homeostasis of the brain microenvironment, and its dysfunction is implicated in the pathogenesis of various neurological diseases, including MS. The BBB consists of multiple biological barriers including the proper blood-brain barrier, the blood-cerebrospinal fluid barrier, and the arachnoid barrier [10][41] (**Figure 1**).

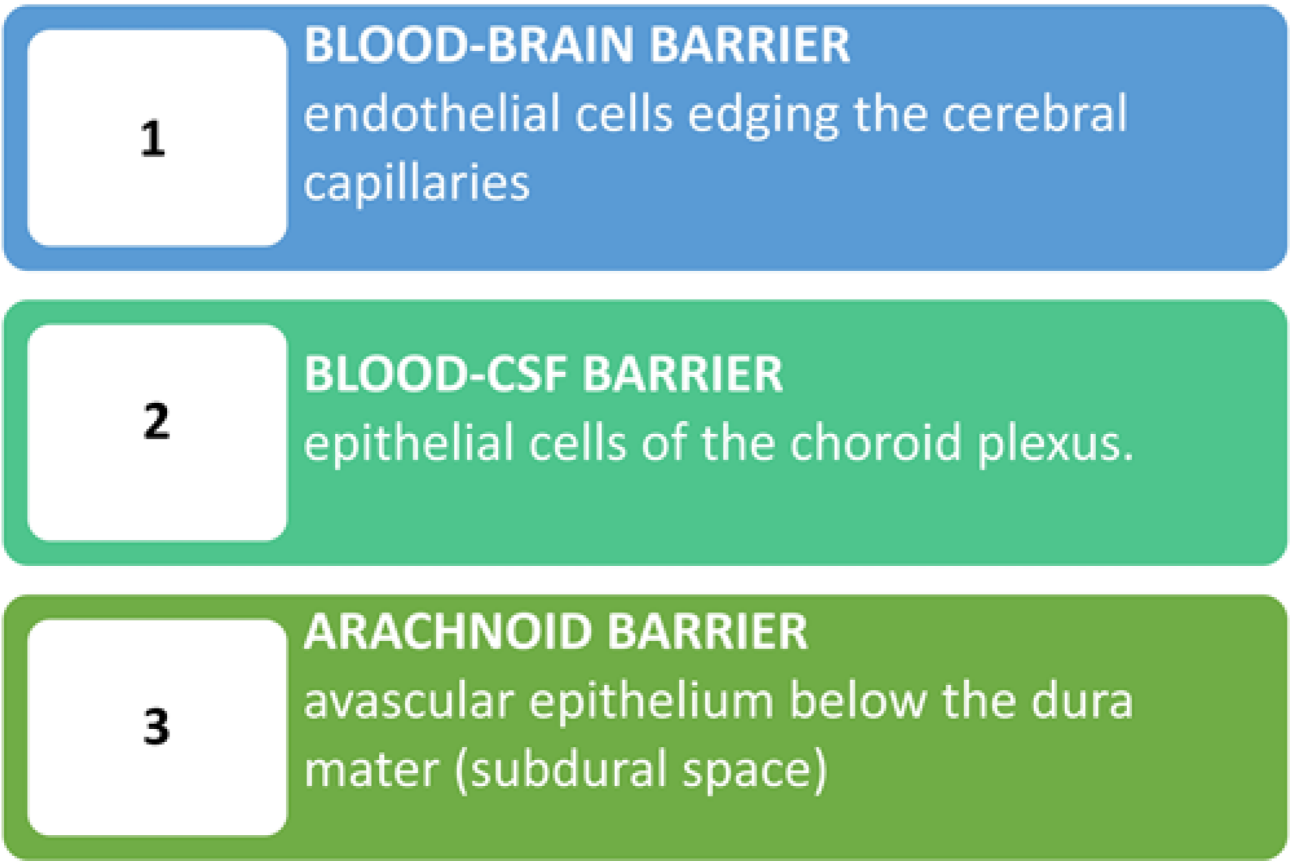

Figure 1. The blood-brain barrier consists of biological barriers formed by different cells at three key interfaces. The 1st layer is made up of microvascular endothelial cells that line the cerebral capillaries and permeate the brain and spinal cord. The 2nd barrier is made up of the epithelial cells of the choroid plexus. This layer, being more permeable to proteins thanks to the presence of a fenestrated endothelium below a cuboidal epithelium, may regulate brain permeability under conditions of gut inflammation. The 3rd barrier is situated below the dura mater and contributes little to blood-brain exchange due to its avascular nature and relatively small surface area compared to other barriers. CSF: Cerebrospinal fluid.

The integrity of the BBB can be influenced by the GM, as bacterial antigens such as lipopolysaccharide (LPS) and SCFAs can travel from the leaky gut to the brain endothelial cells' Toll-like receptors 2 through the bloodstream. In the EAE murine model, high-fat-diet-induced obesity resulted in severe disease accompanied by gut dysbiosis, increased gut permeability, and systemic inflammation, suggesting a role for gut barrier modulation in obesity-induced MS severity [27]. In a similar EAE model, obesity induced by a high-fat diet also led to BBB disruption, which allows the infiltration of monocytes/macrophages and activation of resident microglia, ultimately exacerbating CNS inflammation in EAE [42], likely mediated by IL-6 and CCL-2 [43].

The activation of pro-inflammatory pathways disrupts the delicate balance between protective and harmful reactions. It can induce the release of Vascular Endothelial Growth Factor B/VEGF-B and Tumor Growth Factor/TGF-alpha from microglia, which activates astrocytes and exerts detrimental effects on neurons. The Th17 cytokines IL-17A and IL-17F appear to be pivotal in triggering BBB disturbance [44][45]. As mentioned earlier, SCFAs not only have effects on the colon and peripheral tissues but also play a crucial role in the communication between the GM, gut, and brain. They can cross the BBB through endothelial cell monocarboxylate transporters and a) upregulate the expression of tight junction proteins essential for BBB integrity, b) affect neuroinflammation by influencing glial cell morphology and function, and modulating levels of neurotrophic factors [33]. Moreover, due to its bidirectional nature, GBA neuroinflammation could result in further intestinal inflammation as the disease progresses by affecting efferent cholinergic transmission [2][46][47].

2. Diets and Dietary Supplementations

2.1. Dietary Influence on Multiple Sclerosis

Studies in adults with MS suggest that diet-related inflammation increases the odds of developing the disease [48][49]. The prevalence of Westernized diets, characterized by ultra-processed foods that are high in salt, saturated and trans fatty acids [50] and low in fibers and flavonoids, may contribute to the upregulation of pro-inflammatory compounds, gut dysbiosis, neuroinflammation, and neurodegeneration [51][52][53]. The high salt content in processed foods has been associated with disease exacerbation and the development of new lesions, although the evidence is debated [54][55][56]. Saturated fats activate pro-inflammatory Toll-like receptors (TLRs) and increase NF-κB, which affects the innate immune system [57]. They also play a role in GM-mediated inflammation in MS development and relapse risk, as seen in the EAE model [27][42][43] or in MS patients. [51][53][58].

Conversely, higher fish consumption, particularly oily fish rich in vitamin D and omega-3 fatty acids, is associated with a lower risk of CNS demyelination [59]. Flavonoids, polyphenolic compounds that are abundant in fruits and vegetables, have shown a protective role in MS development in experimental models [60][61]. Non-fermentable cellulose fiber may prevent changes in GM composition and T cell responses associated with CNS autoimmunity in MS [38]. The proper functioning of all players in the gut-brain axis is crucial for managing the impact of MS [**Table 1**].

Several diets have been proposed for MS based on assumptions such as existing food allergies, gluten sensitivity, hypovitaminosis, or the concept of a healthy diet (e.g., Mediterranean diets, Paleolithic diet) [62]. Although a diet rich in fruits and vegetables seems logically protective against relapses and disease progression [63], larger and better-conducted studies are needed to confirm this correlation due to conflicting evidence [64].

Table 1. Synopsis of the main specific diets proposed over time in patients with multiple sclerosis.

Diet Name	Main Characteristics
Allergen free/milk free	Hypoallergenic diet based on the unproven hypothesis of the association between MS and external allergens [65]. The milk protein butyrophilin has been implicated through antigenic mimicry with myelin oligodendrocyte glycoprotein in EAE [66] as well as in MS patients [67]. Some studies with questionnaires suggest an inverse relationship between total dairy intake and MS disability severity [68][69] with an inverse relationship between whole grain intake and MS-related disability [69].
Gluten free	Among studies, only one clinical trial gave meaningful results, but there are methodological limitations [70][71][72]. All in all, the current level of evidence is inadequate to state whether gluten plays a role in MS [71].
Mega Ascorbic	High in vitamin C diet. No well-defined link between MS and vitamin C [73].
Multi Vitaminic	Multi vitaminic supplementation (e.g., A and D): quite convincing data show that higher vitamin intake/serum levels correlate with lower risk of MS development but not convincing on the contrary [74]. Possible detrimental effects of overdosing require vitamin-level monitoring [75][76].
Hebener's	Self-reported disease stability/amelioration in one study with fish oil and antioxidant drugs supplementation + Ω-6 restriction [77].
Kousmine	High in polyunsaturated fats/low in animal fats diet to counteract a possibly increased membrane permeability [78][79][80].
Swank (low saturated fats)	Low-saturated fats (<20 g fat/day or <20% total calories): reported lower death rates and better outcome in the more adherent patients and those with lower disability at entry [81][82].
Mediterranean diets (MD)	Common features include emphasis on vegetables, fruits, beans, nuts, seeds, breads, unrefined grains, and olive oil; inclusion of fish and wine; minimal intake of full-fat dairy products and possibly lean meats [83][84]. Conflicting results on whether lean and unprocessed red meat is detrimental [85][86][87]. It is considered beneficial for its antioxidant properties. Negatively associated with neurological and fatigue symptoms. Adherence should be monitored through validated tests [e.g., Predimed for adults [83] and KidMed for children [88]
Mediterranean/DASH	It derives from the Mediterranean Dietary Approaches to Stop Hypertension (DASH) [89][90].
MIND	The Mediterranean/Intervention for Neurodegenerative Delay (MIND) is a combination of MD and DASH [89][90][91].
Paleolithic1	Consists of high-quality foods full of nutrients and fiber and with less artificial sugar and salt compared to present-day diets [92]. Nutrients included in this diet are essential to myelin growth and repair. Typically, it does not permit consumption of dairy or grain products.
Modified Paleolithic (MD-PI intervention)	This diet is rich in α-lipoic acid and polyphenols. It has commonalities with MD including avoidance of high-fat meats/ultra-processed foods with added sugar,

Diet Name	Main Characteristics
	sodium, and hydrogenated fats [93][94][95].
Wahls™ Paleo diet	Differences from a traditional Paleo diet: exclusion of eggs; limited animal and fish protein. It allows legumes (e.g., soy milk), two servings of gluten-free grains (e.g., rice) per week; it specifies nine cups of fruits and vegetables (F/V)/day with 1/3 each from dark-green leafy vegetables, sulfur-rich vegetables, and deeply colored F/V; seaweed, algae and nutritional yeast are encouraged [96][97].
Wahls/Elim Paleo	This is a paleo version modified by adding a restriction of lectins to reduce intestinal permeability and CNS inflammation [96][97].
Overcoming MS (OMS)	Minimized saturated fats and plant-based, whole-food diet plus seafood [68][98].
Ketogenic diet (KD)	Eliminating all/almost all carbohydrates and increasing the intake of proteins. KD combined with a modified MD have been suggested to improve neuroinflammation in MS [99][100].
Energy restriction (ER)	Chronic ER/Intermittent energy restriction (IER) determines a switch from glucose to fatty acids and ketones as the major fuel source for cells [101][102][103][104]. Mice fed a "fasting mimicking" diet (very low-calorie diet lasting for 3 days every 7 days) exhibited delayed onset, reduced incidence, and decreased severity of EAE. Histological findings show reduced immune cell infiltration and demyelination in the spinal cord [105].
McDougall Diet	A low-fat (10–15% of calories from fat), starch-based, vegan diet with no oils permitted. For 7 days, produced significant favorable changes in commonly tested biomarkers used to predict future risks for cardiovascular disease and metabolic diseases [64][106]. It appeared safe and effective in preventing clinical attacks/new MRI lesions. Drawback = long-term adherence [107].

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teriflunomide) also have anti-inflammatory and antioxidant effects and can shape GM and inhibit the growth of neurotoxin-secreting gut bacteria. [112] Regular exercise has been shown to have positive effects on sleep, depression, paresthesia, fatigue, and cognitive performance [113][114]. However, the impact of physical activity on GM composition and microbial metabolites in the gastrointestinal tract in MS patients remains to be studied [115].

Abbreviations: DASH, Dietary Approaches to Stop Hypertension; ER, Energy restriction; F/V, fruit and vegetables; KD, Ketogenic diet; MD, Mediterranean diet; MIND, Mediterranean/Intervention for Neurodegenerative Delay; MS, multiple sclerosis; OMS Overcoming MS; PI, Paleolithic intervention.

Other factors, such as socioeconomic status, quality of life, and personal motivation, may contribute to the uncertainty surrounding diet-related results. Adherence to an MS-specific diet is associated with higher socioeconomic status, better quality of life, and higher nutritional quality [116]. Enhancing personal motivation and ensuring positive support from study staff and family members are opportunities for future dietary intervention studies in MS, as they can improve adherence and reduce attrition [107][117]. Additionally, strategies should be developed to tailor study diets to the preferences of both individuals with MS and their household members to reduce feelings of burden and improve diet observance [107][117].

Progressive MS disabilities can impact grocery shopping, cooking, and eating, leading to weight loss, isolation, and dysphagia in advanced stages [118][119]. Proper nutritional support and guidance are necessary to ensure a correct diet at any age, starting from the early stages of the disease [109][120][121][122]. On the other hand, an unbalanced diet coupled with reduced physical activity can result in overweight/obesity, which triggers EAE and MS onset and

progression [5][42][43][123][124][125][126][127]. Overweight and obesity are also associated with cardiovascular disease, which contributes to more rapid disability progression in MS [128][129][130].

Considering the role of GM in MS onset and progression, probiotics are of great interest [131]. Probiotic supplementation can modify GM composition and intestinal barrier function, potentially modulating GBA pathways, immune cells, and inflammatory cytokines. Studies in MS patients and animal models have shown promising but inconclusive results, including slower disability progression, reduced depressive symptoms, and improvements in general health [132][133]. Further research is needed to explore different strains and their effects on GM composition, as they may depend on ongoing diets and therapies [134][135][136][137].

2.2. Dietary Supplementations

Apart from probiotics, dietary supplementation of several compounds proposed to increase anti-inflammatory and antioxidant activities have been reviewed by a recent Cochrane metanalysis including 30 randomized controlled trials (RCT) or controlled clinical trials (CCT) among participants with MS on MS-related outcomes, i.e., relapses, disability progression, and magnetic resonance imaging (MRI) measures [138]. After reviewing dietary programs including supplementation to increase PUFAs [comparing PUFAs vs. MUFA or PUFA Omega 6 vs. Omega 3] and other dietary supplements (e.g., antioxidants, acetyl L-carnitine, biotin, creatine, riboflavin), the metanalysis concluded that, at present, there is insufficient evidence to determine whether supplementation with antioxidants or other dietary interventions has any real impact, whether beneficial or harmful, on MS-related outcomes [138][139]. These data confirmed others' conclusions that the body of present evidence is primarily focused around the isolation of individual nutrients, many of which demonstrate no clear effect on major outcomes of MS progression [140]. Of note, although some uncertainties can depend on the dosages used and/or the duration of the treatments (e.g., PUFA), supplementations with other compounds (e.g., vitamin D) may depend on patients' pre-existing nutritional adequacy as opposed to a need for high-dose supplementation [140]. Recent data confirm that although there are no statistically significant correlations between clinical outcomes and vitamin D serum levels or supplementations, patients receiving vitamin D had fewer new T2-weighted lesions, especially when optimal or higher levels of vitamin D (>30 ng/mL) were maintained throughout the entire 4-month observation period [141]. All in all, stronger studies focused on food and nutritional supplementation are required to strengthen the evidence.

2.3 Pediatric issues: Diet and Nutrition Related Issues in Pediatric-Onset Multiple Sclerosis

MS starting in childhood (Pediatric-Onset MS, POMS) is estimated to account for between 2–5% and 5–10% of the MS population worldwide. Although youth with POMS have a lower risk of disability within the first 10 years of diagnosis than those with adult-onset MS, the disease may negatively affect their school and emotional spheres. Moreover, they reach disability milestones earlier than adults, even though they tend to take a longer time to advance to the secondary progressive phase. Overall, quite common cognitive impairment requiring specific management, decrease in QOL, and an increase in economic burden in POMS have been shown to have profound impacts not only on patients but also on their families.

Childhood obesity has been identified as a potential risk factor for increased morbidity not only due to hepatic-cardiac-metabolic comorbidities but also from MS and clinically isolated syndrome (CIS) in adolescents, particularly in girls. The underlying mechanism may involve vitamin D deficiency, as obesity is associated with lower vitamin D levels. Of note, sedentary indoor lifestyles and reduced sunlight exposure, contribute to decreased vitamin D synthesis and increased hypovitaminosis D in children.

Unbalanced diets with increased fats, especially saturated fat content, are associated with a higher risk of unfavorable disease progression. A healthy diet characterized by the consumption of fruit, yogurt and legumes during childhood, appears associated with a lower probability of developing subsequent MS in adulthood. Specific dietary strategies may therefore aid children with POMS in slowing disease progression and improving their quality of life. Overall, these data are particularly worrying if one considers that a large proportion of adolescents with POMS have been found to have a non-self-perceived elevated BMI. To improve their disease progression, they should therefore receive more accurate counseling to improve their diet and physical activity as well.

The gut microbiota (GM) has been implicated also in POMS. Differences in microbial composition and metabolic pathways have been observed in children with POMS compared to healthy controls, and have been found to predict the likelihood of recurrence.

3. Perspectives

What is around the gastrointestinal/nutritional corner of MS ? A) Next generation (NG) engineered probiotics, obtained by modifying original probiotics through gene editing modalities, have hitherto been used in inflammatory bowel disease, and in a number of bacterial infections, tumors, and metabolic diseases, mainly in MS akin EAE murine models and/or in vitro. Promising preliminary results showing they are effective, with fewer side effects than traditional treatments or wild-type strains, suggest that they will probably be proposed soon for central nervous system (CNS) diseases as well, including much probably MS. Of note, the design of NG probiotics should specifically be directed towards the production of metabolites (e.g., SCFAs) and neurotransmitters (e.g., serotonin, GABA) which are known to affect the neurobiology of CNS inflammatory diseases. B) Fecal microbiota transplantation (FMT) represents a further interesting approach to modulate GM. FMT studies in animal models and in humans with MS are still scarce and preliminary. Some data available from a cohort of RRMS patients show that FMT is safe and was well-tolerated and may have also improved their gut dysbiosis and elevated small intestinal permeability. Moreover, single case reports and a case series in addition to confirming the safety of the treatment, also showed specific clinical improvements in MS-related neurological symptoms.

4. Conclusions

In conclusion, data show that (1) no universal best diet exists, (2) healthy/balanced diets are necessary to safeguard the adequate intake of all essential nutrients, (3) diets with high intakes of fruits, vegetables, whole grains, and lean proteins that limit processed foods, sugar, and saturated fat appear beneficial for their antioxidant

and anti-inflammatory properties and their ability to shape a gut microbiota that respects the gut and brain barriers, (4) obesity may trigger MS onset and/or its less favorable course, especially in pediatric-onset MS. Vitamin D and polyunsaturated fatty acids are the most studied supplements for reducing MS-associated inflammation.

More in detail, several dietary/nutritional factors play an important role both in adult and pediatric MS development and progression. Several gut-oriented nutritional interventions aiming to improve the dysregulation of the so-called Gut Brain Axis through a proper diet appear to intervene beneficially mainly against the inflammatory pathomechanisms associated with MS. The efficacy of any dietary intervention in MS, however, remains difficult to prove due to spontaneous remissions (and relapses) with temporary clinical improvement occurring by chance alone. Pending more solid evidence on specific diets, experts suggest that individuals with MS should be taught to follow a “healthy” regime and possibly enter into nutrition education programs, which, however, are largely lacking as in most other neurological diseases at present.

Because of the high prevalence of overweight/obesity, and the evidence that obesity can worsen MS prognosis, education on weight management is still an unmet need. Pediatric interventions may be hampered by the lack of self-perceived BMI elevation at this age. Because there is, at present, no robust evidence, future research is also needed to identify appropriate study designs and intervention strategies targeting physical activity participation. New solid longitudinal and experimental designs are necessary not only to better elucidate the role of diet and other modifiable lifestyle factors in this population, but also to explore other modalities of support. These should include a closer monitoring of nutritional status of patients with moderate-advanced MS in order to prevent their tendency to be overweight secondary to the decrease in basal energy expenditure and loss of muscle mass.

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