Taylor & Francis
Taylor & Francis Group

Food Reviews International

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/lfri20

Gut microbiota alterations and nutritional intervention in multiple sclerosis disease

Clara Noguera-Navarro, Diana Navas-Carrillo & Esteban Orenes-Piñero

To cite this article: Clara Noguera-Navarro, Diana Navas-Carrillo & Esteban Orenes-Piñero (2022): Gut microbiota alterations and nutritional intervention in multiple sclerosis disease, Food Reviews International, DOI: 10.1080/87559129.2022.2062771

To link to this article: https://doi.org/10.1080/87559129.2022.2062771

Published online: 18 Apr 2022.

FOOD REVIEWS INTERNATIONAL
https://doi.org/10.1080/87559129.2022.2062771

Taylor & Francis
Taylor & Francis Group

Gut microbiota alterations and nutritional intervention in multiple sclerosis disease

Clara Noguera-Navarro[a], Diana Navas-Carrillo[b], and Esteban Orenes-Piñero[a,b]

[a]Department of Biochemistry and Molecular Biology-A, University of Murcia, Murcia, Spain; [b]Department of Surgery, Hospital Clínico Universitario Virgen de la Arrixaca, Murcia, Spain

ABSTRACT

Multiple sclerosis (MS) is a chronic neurodegenerative autoimmune disease characterized by inflammation, demyelination and axonal degeneration. There are different types of MS: Relapsing-Remitting, Primary-Progressive, Progressive-Relapsing and Secondary-Progressive disease. The prevalence of this pathology is about two million people worldwide, affecting at the age of 20–40 years, with predominance in females. The idea of remitting symptoms by modification of gut microbiota has been hypothesize through different studies, and it could have a positive impact in quality of life on these patients. Gut microbiota affects the development and regulation of the immune system, so it could be considered as a new environmental risk factor. Moreover, as a potential risk factor, it could be positively changed by diet, suggesting new therapeutic avenues and creating a protective environment based in microbiota modifications and/or nutritional interventions. Nowadays, there is strong evidence showing a relationship between the immune system and the inflammatory state. Thus, it is of paramount importance to elucidate how gut microbiota could impact on the inflammatory state of MS to improve disease´s symptoms. The aim of this review is to comprehensively analyze the relationship between gut microbiota and the inflammatory state on MS, including a nutritional therapy to calm down the symptoms.

KEYWORDS

Multiple sclerosis; microbiota; dysbiosis; nutritional intervention; inflammation

Introduction

The term human microbiota refers to the presence of diverse microorganisms into several ecosystems in the body (inside and on the surface); whereas microbiome are the genes they encode.[1–3] Human microbiota contains one hundred billion microorganisms; the number of bacteria grow exponentially from the beginning of the small intestine (10^3–10^5 organisms/g) to the end of the large intestine (10^{10}–10^{12} organisms/g).[1,3] The microbiota is involved in different roles, such as influence of host metabolism (nutrition and energy harvest), intestinal epithelial homeostasis, drug metabolism and toxicity, immune system response and protection from pathogens.[4,5] Imbalance microbiota, known as dysbiosis, could develop in obesity, cardiometabolic and neurodegenerative diseases, such as multiple sclerosis (MS).[4,6]

Gut microbiota could be regulated by several factors, such as diet, ethnicity, medication, smoking and gender.[4] It is formed mainly by bacteria, followed by smaller proportions of fungi, virus and *Archea*.[7] The most abundant species (corresponding to the 90% of gut bacteria) are *Bacteroidetes* and *Firmicutes*[2,7] whereas other less abundant species are *Proteobacteria, Actinobacteria, Fusobacteria* and *Verrucomicrobia* phyla, among others.[8] Changes in gut microbiota have been shown in different diseases, such as atherosclerosis (more abundance of *Collinsella* genus compared

CONTACT Esteban Orenes-Piñero eorenes@um.es Department of Biochemistry and Molecular Biology-A, University of Murcia, Avda. de las Fuerzas Armadas, s/n, Lorca, Murcia 30800, España

with healthy people), children with type-1 diabetes (increased *Actinobacteria* while the ratio of *Firmicutes/Bacteroidetes* was decreased) and obesity (lower abundance of genus *Prevotella* while higher abundance of *Clostridium*).[9] This way, disruption of this balance between mutualistic/commensal microorganism and pathobionts (endogenous benign microbes which could generate different pathologies in a transformed ecosystem) has potential pathological consequences on the host health status.[10]

MS is a chronic neurodegenerative autoimmune disease characterized by inflammation, demyelination and axonal degeneration[11] (Fig. 1). It affects both, white and grey matter, in the central nervous system (CNS), by primary demyelination and diffusing damage and neurodegeneration in the brain.[12] MS patients may experience visual disturbances, cognitive and emotional changes (depression, MS-related dementia), movement and balance difficulties (muscle spasms, ataxia), bowel and bladder dysfunction, pain and fatigue.[13,14] There are different types of MS: Relapsing-Remitting disease (RR; associated with frequent inflammatory lesions in the brain and spinal cord with periods of exacerbation followed by remission), representing between 85–90% of the subjects, and Primary-Progressive disease (PP; clinical variant of MS without inflammation) affecting 10–15% of the subjects.[12,15,16] Two more types of MS have been also defined: Progressive-Relapsing disease (PR; a progressive worsening of MS similar to PP) and Secondary-Progressive (SP; PR disease after several years of duration and a moderate level of clinical disability).[12,17] The prevalence of this pathology is about two million people worldwide, affecting at the age of 20–40 years, with predominance in females.[11,18]

Indeed, there is a profound controversy about the aetiology of MS.[11] It has been hypothesized that gut microbiota could be altered in MS, even though the mechanisms have not been conclusively demonstrated in human autoimmune diseases. However, accumulating evidence from animal models has shown that gut microbiota affects the development and regulation of the immune system.[19] Studies have been focused on host immune response effects against pathogens and chronic

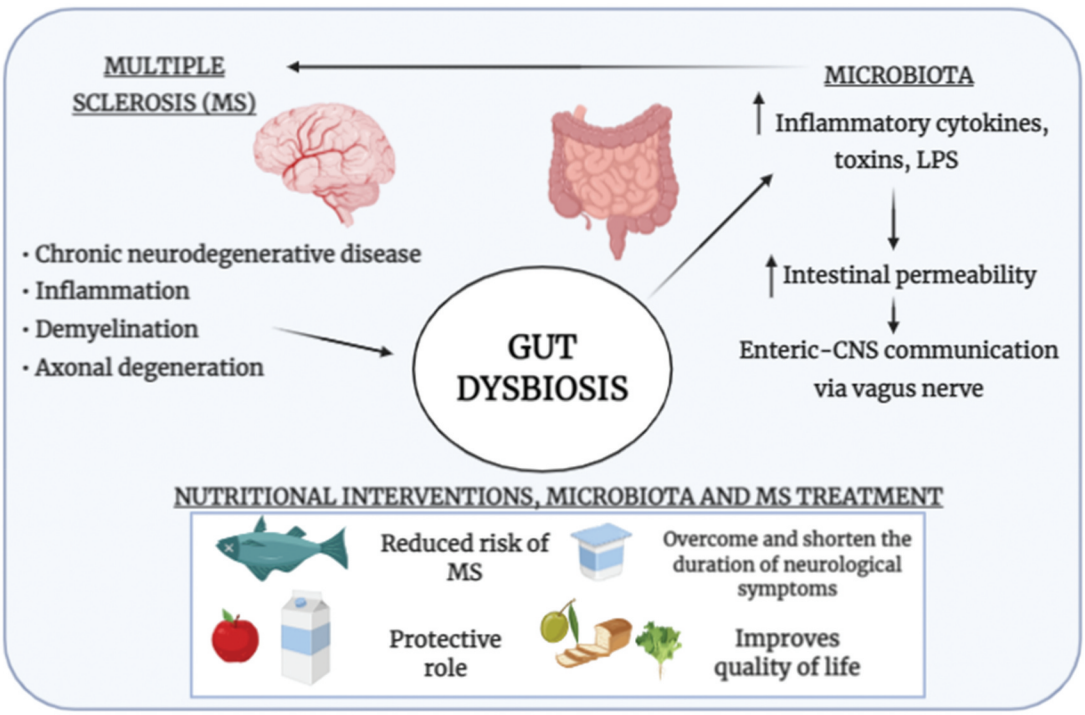

Figure 1. Gut dysbiosis can affect several aspects in the pathophysiology of MS.

inflammatory/autoimmune state of gut microbiota.[20] Thus, the commensal microbiota could be considered as a new environmental risk factor in immune-mediated diseases, such as MS.[16] Interestingly, if gut microbiota could be considered as a risk factor, it could be positively modified by diet,[21] suggesting new therapeutic avenues, as no cure for MS has been discovered so far.[22]

Regarding gut microbiota, it could promote an anti-inflammatory state minimizing the presence of pathogens (protective environment).[23] However, a dysbiosis state could drive to an inappropriate inflammation response and an increased inflammation risk[23] (Fig. 1). Indeed, gut dysbiosis has been previously associated with the development of several immunological diseases such as inflammatory bowel disease (IBD), coeliac disease, rheumatoid arthritis, type-1 diabetes and asthma, among others.[24] MS is a neurodegenerative disease aggravated by an inflammatory process,[12] so a potential therapy target should be the inflammatory component of the disease.[15] Although it is widely known that immune mechanisms and inflammation are the key of the pathogenesis of MS, it is still debated which one is the initial event.[25] Thus, the aim of this review is to analyze the relation between gut microbiota and the inflammatory state on MS, including a nutritional therapy to calm down the symptoms.

Materials and methods

Published data from this review were identified by search and selection database of PubMed, Elsevier and Science Direct. Reference lists from relevant articles, reviews and books on the subject were obtained. Searching was made in two steps. First, a quest was made by relating the keywords "multiple sclerosis" with "gut microbiota", "inflammation", "nutritional treatment" and "immune system". Secondly, the relationship among MS and several treatments using microbiota was evaluated, adding them to a second selection with the keywords: "gut microbiota", "immune system", "pro-prebiotics treatment" and "faecal transplantation".

Multiple Sclerosis (MS)

There are different specific pathological changes in MS which triggers into a chronic inflammatory process. At this point, focal lesions (in the white and grey matter, the deep brain stem nuclei and the spinal cord) with primary demyelination and astrocytic scarring are the pathological modifications that appear at the beginning of this disease.[12] Primary demyelination means that oligodendrocytes and myelin sheaths are destroyed, preserving the axons of the neuron. Diffuse neurodegeneration is present as well, resulting in brain atrophy, reflected by the loss of brain and spinal cord volume. Even though these are general changes present in MS patients, their contribution to the global pathology varies between different patients and stages of the disease.[12]

Environmental and genetic susceptibility exposures have been also incriminated. Neither auto-antigens nor infectious agents have been completely associated with MS. However, the similarity of MS susceptibility genes with other autoimmune disorders considers this disease as a primary-organ specific autoimmune disease.[25] The pathogenic cascade initiates with the autoreactive lymphocytes (activated T and B cells) that gain access to the CNS through a damaged blood-brain barrier (BBB) (Fig. 2), thus culminating with different changes that occur during MS disease.[26] Depending on the location of the lesions, MS could have from one to different symptoms (optic neuritis, brainstem and spinal cord syndromes, cortical presentations ...).[27] Pain is also included, and can be defined as primary pain (caused by inflammation, demyelination or neurodegeneration) or secondary pain (due to indirect consequences of the CNS lesions).[14] MS relapses could last from hours to days.[27]

A good MS biomarker could be defined as one that should be easily and reliably measured, should have high sensitivity and specificity, should correlate with the disease biology and/or pathogenesis and should be cost effective. Predictive biomarkers should identify individuals at risk of developing MS; whereas diagnostic biomarkers could distinguish MS from other diseases. On the other hand, disease

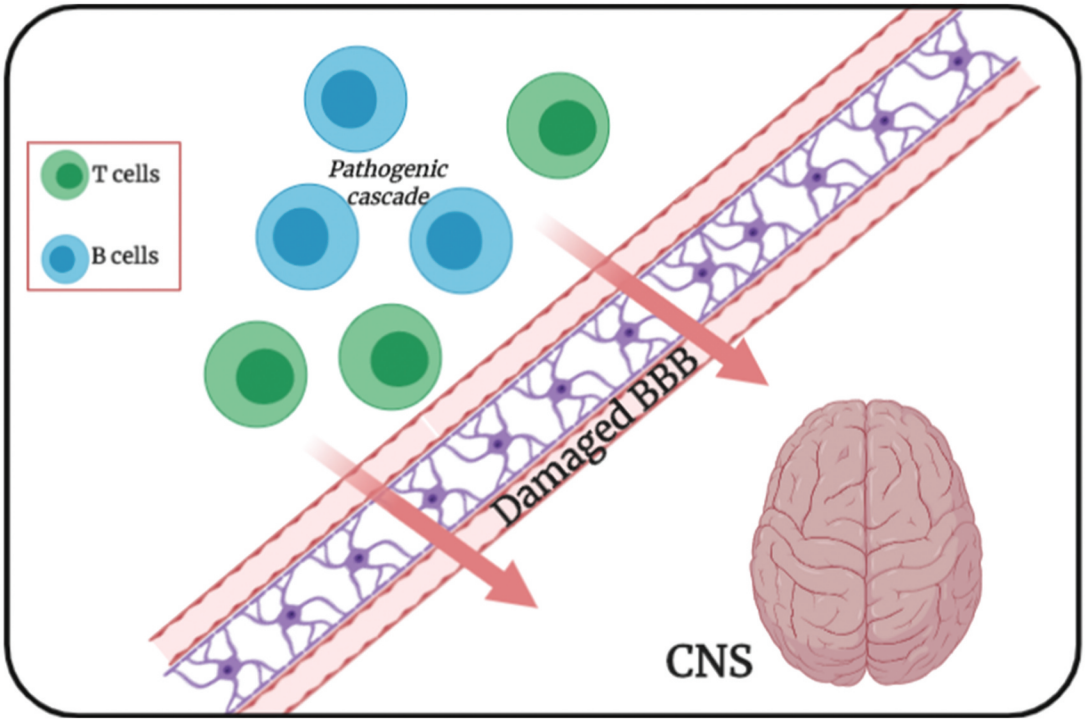

Figure 2. Schematic image showing the pathogenic cascade initialization with the autoreactive lymphocytes (activated T and B cells) gaining access to the CNS through a damaged BBB.

activity biomarkers could distinguish the different types of MS.[11] The most important tool used in MS is magnetic resonance image (MRI) with a contrast enhancing technique, allowing the observation of different biomarkers as hyperintense T2-weighted lesions, grey matter atrophy, whole brain atrophy and spinal cord atrophy.[11]

In a progressive disease, pronounced inflammation is mainly observed, but in patients with stable disease or at very late stages of the disease, tissue infiltration by leukocytes may decrease.[12] Active inflammation and disruption of the BBB have been detected in MS patients, impairing its integrity throughout the course of MS.[28,29] The inflammatory activity is associated with leukocytes, reactive astrocytes, microglia and myelin-laden macrophages in several combinations. The rudimentary CNS lymphatic system associated with the dural venous sinuses allows the migration of dendritic, T and memory B-cells as a consequence of chronic CNS inflammation.[28]

T-cells can be transmigrated across CNS endothelium of postcapillary blood vessels. CD4+ T cells contribute to the initiation of the immune response in MS patients and CD8+ T cells have been identified as a potential major contributor to MS pathology.[12,14,28,30] B-cells are a major component of the adaptive immune inflammation in the brain and spinal cord of MS patients, but their role remains unclear due to contradictory reports.[12] Interestingly, the amelioration of inflammation have been related with plasma blasts and plasma cells (developed from B-cells) because both of them express Interleukin-10 (IL-10) within MS lesions.[12,28] The initial source of oxidative injury in MS is mediated by macrophages and microglia oxidative activation. Several growth factor receptors have also demonstrated their importance in the oxidative process such as epidermal growth factor receptor (EGFR) and platelet derived growth factor receptor (PDGFR).[29]

Microbiota dysbiosis could lead to the inflammatory activation of the immune system. Specifically, it has been found that the gut microbiota influenced the interaction between *T*-cell C-C chemokine receptor type 9 (CCR9) and its ligand chemokine (CCL25). This interaction plays a role in *T*-cell development and in immunity in the small intestine epithelium. A decrease of the CCR9 functionality

Table 1. Bacteria genera increased and decreased in MS patients.

Increased	Decreased
• *Acidaminococcus*	• Adlercreutzia
• *Acinetobacter*	• Aquamonas
• *Actinomyces*	• Bacillus
• *Akkermansia*	• Bacteroides
• *Anaerococcus*	• Clostridium
• *Anaerostipes*	• Faecalibacterium
• *Atopobium*	• Lachnospira
• *Catenibacterium*	• Lactobacillus
• *Citrobacter*	• Parabacteroides
• *Cloacibacillus*	
• *Eggerthella*	
• *Enterobacter*	
• *Ruminococcus*	
• *Streptococcus*	

was observed in patients with RR-MS and SP-MS. The blockade of the CCR9–CCL25 interaction reduced CCR9+ CD4+ T memory cells in peripheral blood.[16] Moreover, antibiotic treatment increased CCR9+ T memory cells in SPF mice, thus confirming the influence of the gut microbiota in CCR9+ T memory cells.[16]

Although there is some controversy, it could be said that microbiota species richness is reduced in MS patients with active disease but not in MS patients in remission.[19] In MS patients, some bacteria genera can be increased, such as: *Acidaminococcus, Acinetobacter, Actinomyces, Akkermansia, Anaerococcus, Anaerostipes, Atopobium, Catenibacterium, Citrobacter, Cloacibacillus, Eggerthella, Enterobacter, Ruminococcus and Streptococcus;* whereas other bacteria gender can be decreased, such as: *Adlercreutzia, Aquamonas, Bacillus, Bacteroides, Clostridium, Faecalibacterium, Lachnospira, Lactobacillus and Parabacteroides*[2] (Table 1).

On the other hand, the anti-inflammatory effect of short-chain fatty acids (SCFA) (produced by intestinal microbes) have been widely elucidated.[31] The administration of living bacteria as probiotics or the metabolites they produced as prebiotics have been observed to reverse the loss of BBB integrity.[32] In a comparative study of germ-free (GF) mice, that is, without intestinal microbiota, with specific pathogen-free (SPF) mice, it was observed that GF rodents showed greater blood–brain barrier (BBB) and intestinal permeability compared to those of the SPF group, thus predisposing them to the development of Alzheimer's disease.[32] Mice were injected intravenously with Evans Blue dye (red) and an extravasation was observed in different regions of the brain in GF mice due to the high permeability of the BBB. To confirm that this higher permeability was associated with the absence of microbiota, these GF mice were colonized with the microorganisms *Clostridium tyrobutyricum*, that produces mainly butyrate or with *Bacteroides thetaiotaomicron*, which produces mainly acetate and propionate. Interestingly, colonized GF mice restored the impermeability of the BBB and a significant decrease of Evans Blue dye was found in the three different areas of the brain. Furthermore, the same result was observed when GF mice were treated with sodium butyrate alone by oral gavage for 3 days. This administration was associated with an increased expression of occludin (integral membrane protein of tight junctions) in the frontal cortex and hippocampus, and therefore, with a decrease in the dye extravasation.[32] These results show the importance of the intestinal microbiota in the integrity of the BBB.

Microbiota: Composition and Characteristics

After birth, the gut is rapidly colonized by trillions of normally non-pathogenic bacteria. Babies born trough vaginal via got colonies similar to their mother´s vaginal microbiome.[1,3,33] These colonies play a beneficial role in babies´ digestion while those babies born via caesarean section would acquire

potentially harmful bacteria colonies similar to those present in the skin surface of the mother.[1] Moreover, it has been observed that in preterm neonate, the diversity of microbiota was reduced when compared with full-term children.[3] The divergence of gut microbial will increase with time, remaining relatively stable in healthy individuals.[33] It has been previously observed that 90% of healthy gut microbiota belongs to the *Bacteroidetes* (*Bacteroides and Prevotella*) and *Firmicutes* (*Clostridium, Eubacterium and Ruminococcus)* Phyla. In fact, healthy individuals contained *Bacteroidaceae, Clostridiaceae, Prevotellaceae, Eubacteriaceae, Enterobacteriaceae, Saccharomycetaceae* and *Methanobacteriaceae* bacterial families.[34,35] These organisms are involved in complex biochemical interactions with their host, which upkeep sort of variations related with genome and lifestyle factors (diet, drugs and environmental exposure).[33]

Depending on the different parts of the gastrointestinal tract, there is a different environment which allows the growth of specific microbiota. In the stomach (full of acid-resistant bacterial strains), predominantly inhabit *Firmicutes, Bacteroidetes, Actinobacteria, Fusobacteria* and *Proteobacteria* with the bacterial genera *Prevotella, Streptococcus, Veillonella, Rothia and Haemophilus*.[34] The small intestine is divided into three parts, duodenum, jejunum and ileum. The duodenum (bile acids, pancreatic secretions and antimicrobial agents) is inhabited by *Firmicutes and Actinobacteria*. The jejunum is mainly inhabited by *Lactobacilli, Enterococci and Streptococci*. The closed ilium is full of aerobic species and distal ileum is populated with anaerobes and Gram-negative organisms similar to the colon[34] (Fig. 3). The large intestine (predominant site of water absorption and fermentation of undigested food) is mainly inhabited by *Firmicutes and Bacteroidetes*. The lumen of large intestine is associated to bacteria genera such as *Bacteroides, Bifidobacterium, Streptococcus, Enterobacteriaceae, Enterococcus, Clostridium, Lactobacillus and Ruminococcus;* whereas the mucosa is associated to *Clostridium, Lactobacillus, Enterococcus and Akkermansia*[34] (Fig. 4).

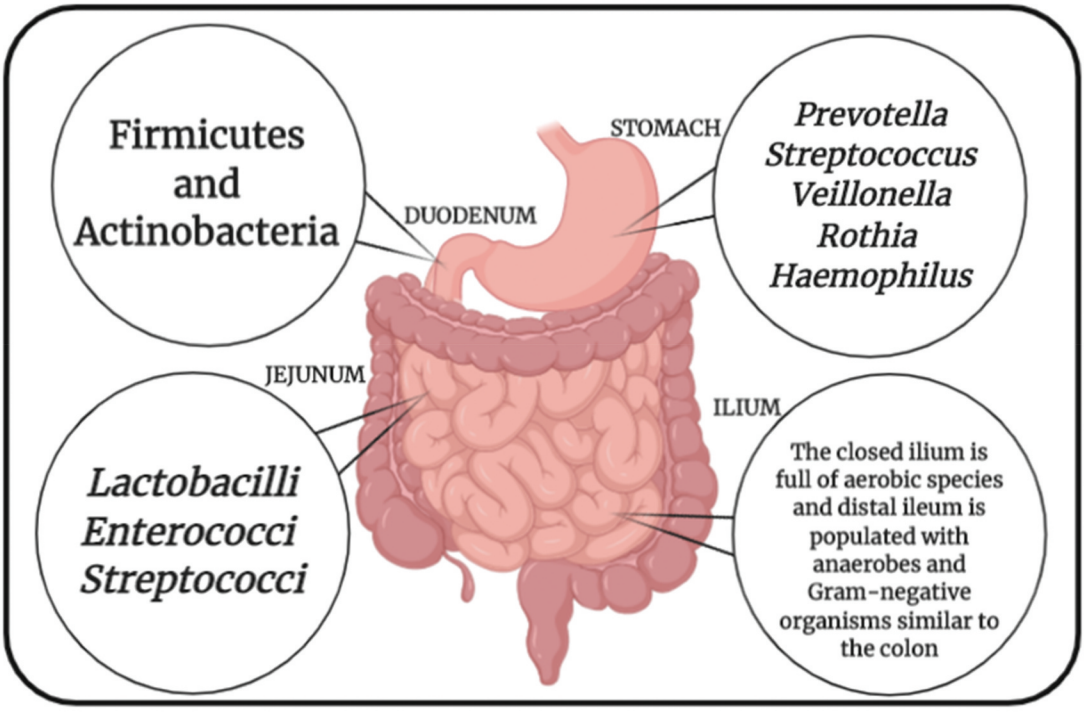

Figure 3. Bacterial genera that predominantly inhabit in the stomach (*Prevotella, Streptococcus, Veillonella, Rothia and Haemophilus*), duodenum (Firmicutes and Actinobacteria), jejunum (*Lactobacilli, Enterococci and Streptococci*) and ilium (the closed ilium is full of aerobic species and distal ileum is populated with anaerobes and Gram-negative organisms similar to the colon).

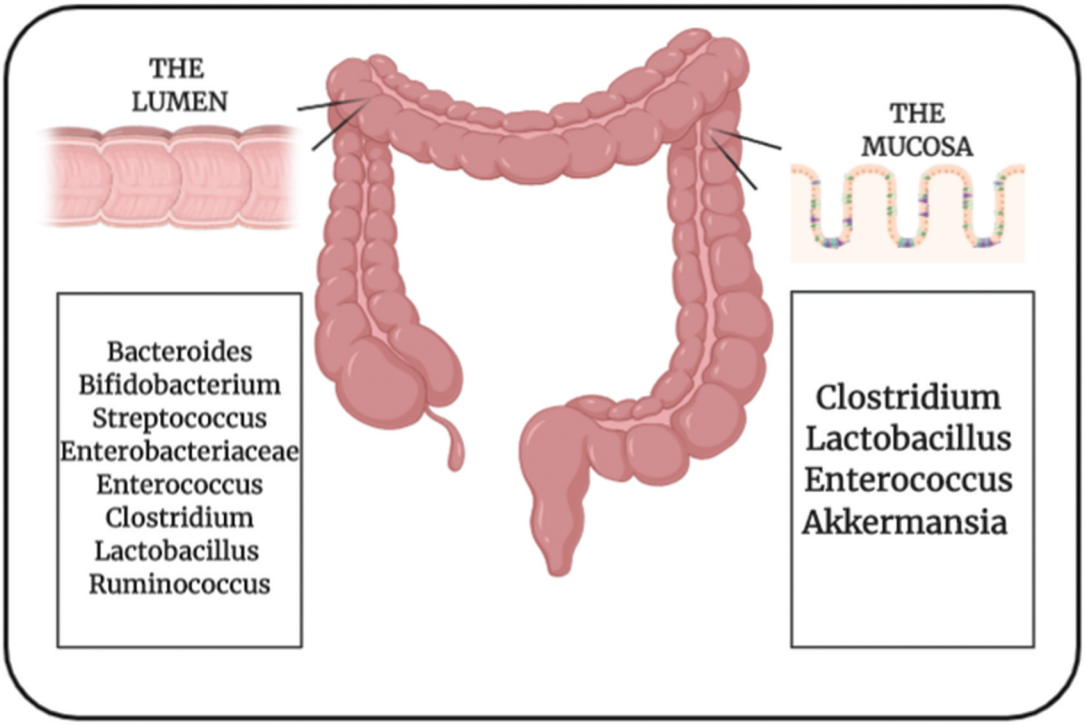

Figure 4. Bacterial genera that inhabit in the lumen (*Bacteroides, Bifidobacterium, Streptococcus, Enterobacteriaceae, Enterococcus, Clostridium, Lactobacillus and Ruminococcus*) and the mucosa (*Clostridium, Lactobacillus, Enterococcus and Akkermansia*) of the large intestine.

The mechanisms of signal transmission between the brain and the bowel are complex and not completely elucidated, but they include neural, endocrine, immune and metabolic pathways (lipopolysaccharide (LPS), intestinal peptides, hormones . . .).[35] The enteric-nervous system (ENS), mostly defined as the second brain, includes a large group of neurons and neuron protective glia cells.[36] The ENS is a web of sensory neurons, motor neurons, and interneurons embedded in the wall of the gastrointestinal system, stretching from the lower third of the oesophagus right through to the rectum. The ENS is protected by a blood–ganglion barrier. Glial cells are key players in the protection against injuries. Indeed, enteric glia exerts a critical role in ENS maintenance and survival as well as in the cross-talk between ENS and the immune system. *In vitro*, enteric glial cells are stimulated by proinflammatory cytokines and in response, release cytokines including interleukin-6.[37]

Microbiota ferments carbohydrates and digestible oligosaccharides. In addition, it synthesizes SCFA (butyrate, propionate and acetate), vitamins B and K, niacin, biotin and folate.[38] Microbiota contributes to gut immunomodulation producing microbial-associated molecular patterns (MAMPS), which are essential structures that build the first line of defence for the microbes. In addition, microbiota antagonizes pathogenic bacteria due to the production of antimicrobial factors and promoting colonization resistance which avoids, as a result, this undesirable bacterial growth.[38] Healthy microbiota has been associated with improved learning/memory and behavioural flexibility. In contrast, a worst microbiota´s profile generates a milieu of signalling molecules that can communicate with the brain modulating its function, behaviour and cognition.[6] Thus, bacteria and their metabolites may affect through vague nerve stimulation or through immune-neuroendocrine mechanisms.[38]

Due to constant exposure to microbial antigens, the intestine is constantly at high risk of barrier dysfunction.[33] The gut-associated lymphoid tissue (GALT) is the gut´s own immune system of the organism. Impaired intestinal barrier function leads to the increase of circulating toxins and LPS,

driving to inflammation. In addition, the increase of circulating inflammatory cytokines, such as TNFα, IL-6 and C-reactive protein (CRP) are involved on intestinal permeability.[33] There are different hypotheses trying to explain the link between chronic intestinal inflammation and neurodegeneration, some of them include the imbalance of pro- and anti-inflammatory gut microbes, systemic inflammation and the influence of microbial amyloids on host amyloidosis.[39]

Gastrointestinal lamina propria and GALT represent the mucosal immune system (protective immunity). The interaction between macrophages with MAMPs stimulates the production of IL-1β. This proinflammatory cytokine maintains regulatory *T*-cells homeostasis and oral tolerance to dietary antigens.[39] In addition, gut microorganisms activate *T*-cells and B-cells and also promote the release of several immunoglobulins, limiting inflammatory responses.[39] Moreover, the maintenance of immune homeostasis and an adequate inflammation response is mediated by *T*-cells. If all these functions are missing, inflammation can be initiated.[37] Microbial dysbiosis induces inflammatory responses mediated by T helper 1 (TH1), TH2 (both facilitate the expression of pro-inflammatory cytokines) and Th17 cells (induce secretion of antimicrobial peptides (AMPs) and the synthesis of immunoglobulin A (IgA).[2,34]

On the other hand, probiotics are living microorganisms that promote gut health and potentially modulate dysbiosis. Their beneficial effects mostly depend on their metabolism and metabolic by-products which finally activate immune responses.[10] Different strains of *Lactobacillus* and *Bifidobacterium* showed the capability to reduce pro-inflammatory IL-6 and IL-7 levels, to restore the Treg/Th17 balance and to control the overgrowth of *Enterobacteriaceae* pathobionts.[10] Probiotics also increase the integrity and enhancement of the epithelial barrier; inhibit the adhesion of pathogens to the intestinal mucosa and eliminate pathogens through the production of antimicrobial substances.[3] As far as we know, health benefits have mainly been demonstrated for specific probiotic strains of the following genera: *Lactobacillus sp, Bifidobacterium sp, Saccharomyces sp, Enterococcus sp, Streptococcus sp, Pediococcus sp, Leuconostoc sp, Bacillus sp* and *Escherichia coli*.[34]

Prebiotics are non-microbial and non-digestible dietary compounds that stimulate the growth and activity of probiotics.[33] They are fermented by colonic anaerobic bacteria to produce important metabolites for host physiology.[10] There are many types of prebiotics, being most of them oligosaccharide carbohydrates (OSCs); although some novel observations evidenced that prebiotics are not only carbohydrates.[40] Fructo-oligosaccharides (FOS) and galacto-oligosaccharides (GOS) are the two most important groups of prebiotics with beneficial effects on human health. Prebiotics can be divided in 5 groups: 1) Fructans (inulin and FOS), 2) galacto-oligosaccharides (products of lactose extension), 3) Starch and Glucose-Derived Oligosaccharides (upper digestion resistant starch and polydextrose), 4) Other Oligosaccharides (pectic oligosaccharide (POS)) and 5) Non-Carbohydrate Oligosaccharides (cocoa-derived flavanols and polyphenols).[40] Importantly, animal studies have provided strong evidence that prebiotics can modulate gut microbiota, but in humans this relation is more controversial.

Faecal microbiota transplantation (FMT) is the procedure of transferring the microbial ecology from a healthy donor into a patient affected by microbial dysbiosis. Nowadays, it has proved to be highly successful in treating *Clostridium difficile* infection. Therapeutic FMT reduces pro-inflammatory cytokines and initiates the restoration of intestinal homeostasis.[10] Currently, FMT has been experimentally used to treat colitis, constipation, intestine bowel disease, Parkinson's disease and multiple sclerosis.[34]

MS and Inflammation

There are several studies analyzing the impact of inflammation in MS disease (Table 2). In one study including 52 patients with RRMS (18 patients), PPMS (5 patients), another neurological diseases (19 patients) and with no diagnosis (10 patients) it was analyzed if MS patients would display a greater cerebrospinal fluid (CSF) enrichment in highly differentiated CD8+ T cells as compared to patients

Table 2. Studies associating MS and inflammation.

Sample	Purpose of the study	Results	References
18 RRMS 5 PPMS 19 AND 10 no diagnosis	Role of CD8+/CD4+ to distinguish RRMS from the other types of MS	CD8+ T cells and inflammation may play an important role in MS.	[41]
43 RRMS 10 RA 47 healthy donors	Identify differentially expressed genes in MS	Elevation of CD8 T cells in MS patients. Higher production of IL-17 in MS patients.	[42]
35 MS 67 controls	Analyse in detail the phenotype and activation state of T and B lymphocytes in MS	Higher T cells proliferation in acute and relapsing MS. B cells enriched in MS.	[43]
22 HC 12 elderly HC 33 RRMS 34 SPMS 13 NO 17 NI-NIND	Demonstrate the potential of human CCR9 +CD4+ memory T cells in the regulation of the acute autoimmune inflammation associated with RRMS or neuromyelitis optica	Reduced trend of CCR9 in RRMS and SPMS compared with the rest of patients and controls. CCR9 Tm cells could exhibit anti-inflammatory and neuroprotective effects.	[44]
547 MS 1057 controls	Investigate the potential role of environmental factors including lifestyle, medical and nutritional factor on MS onset.	More inflammatory diet was associated with a significant increase in the risk of MS ($p < .001$).	[45]

Abbreviations: AND: Another Neurological Diseases; HC: Healthy Controls; MS: Multiple Sclerosis; NI-NIND: non inflammatory-non immunological neurodegenerative disease; NO: Neuromyelitis Optical; RA: Rheumatoid Arthritis; RRMS: Relapsing-Remitting Multiple Sclerosis; SPMS: Secondary-Progressive Multiple Sclerosis.

with another neurological diseases.[41] The results elucidated that in RRMS patients, the median CSF enrichment in CD8+ T cells was significantly higher than in CD4+ T cells ($p = .024$). This CSF enrichment was also significantly higher in RRMS patients than in PPMS and another neurological diseases patients ($p = .006$). So, the data suggested that whereas CD8+ T cells seem to play a role in RRMS, it is different for PPMS patients. Importantly, it has been observed that CD8+ T cells have cytotoxic activity towards neurons and oligodendrocytes by axonal loss in MS lesions.[41] Another study with 43 RRMS patients, 10 rheumatoid arthritis patients and 47 healthy donors, reported an elevation of CD8+ T cells with the surface expression of CD161 in MS patients compared with healthy donors ($p = .03$).[41] In addition, CD8+ T cells produced higher levels of IL-17 in MS patients than in healthy donors ($p = .04$),[42] showing the importance of an inflammatory state in MS disease.

In another study, 35 MS patients (acute MS, RRMS, SPMS and PPMS) and 67 controls (disseminated encephalomyelitis, Rasmussen´s encephalitis, progressive multifocal leukoencephalopathy, stroke, Alzheimer´s disease and age-matched controls) were compared.[43] The clinical course of MS was defined by a certified neurologist. Inflammatory control cases were selected with active lesions characterized by profound brain inflammation and disease-specific tissue injury. In addition, no inflammatory control cases were included (patients with acute ischaemic stroke lesions and advanced Alzheimer´s disease). And finally, normal controls were also included with no neurological disease and absence of neuropathological lesions. T cells proliferation was higher in lesions of acute and relapsing MS compared to progressive MS ($p < .01$) and B cells were more selectively enriched in MS lesions in comparison to other inflammatory controls ($p < .001$), taking part in the adaptive immune inflammation in the brain and spinal cord of MS patients.[43]

More recently, the expression of CCR9 as a receptor of CD4+ T cells was elucidated in 22 healthy controls, 12 elderly healthy controls, 33 RRMS patients, 34 SPMS patients, 13 neuromyelitis optica patients and 17 non-inflammatory-non immunological neurodegenerative disease patients.[44] In all cases, the diagnosis was made by board-certified neurologists and the differential diagnoses of RRMS, SPMS and neuromyelitis optica were established according to the McDonald or Wingerchuk diagnostic criteria. Specifically, SPMS diagnosis was based on a history of gradual worsening of the disease after an initial relapse. The study showed a reduced trend in MS patients (RRMS and SPMS) of CCR9 when compared with the rest of patients and controls ($p < .01$). Importantly, it was found that CCR9

Tm cells could exhibit anti-inflammatory and neuroprotective effects, might be a potential diagnostic marker for SPMS and might be also employed as a potential therapeutic target for MS.[43] In a more recent study, a population-based incident case-control study aimed to investigate the potential role of environmental factors including lifestyle, medical and nutritional factors on MS onset.[45] 547 MS patients and 1057 controls filled a Food Frequency Questionnaire (FFQ) for calculating Dietary Inflammatory Index (DII) and to determine the inflammatory characteristics of diet. Higher negative DII scores implied more anti-inflammatory diets while higher positive DII values indicated a more pro-inflammatory nature of diet. The increased of energy adjusted-DII through quartiles (more inflammatory diet) was associated with an increase in the risk of MS ($p < .001$).[45] The results of the study support a significant risk factor role of high DII score for MS onset.

Gut microbiota dysbiosis and MS

Importantly, there are some controversies about the richness of gut microbiota in MS patients. These discrepancies have been previously associated with the importance of phenotypic subcategorization in MS.[19] There are a number of studies in the bibliography analyzing the impact of microbiota in the treatment of MS (Table 3). One study, including 20 MS patients and 58 healthy controls, was performed to indicate an association between altered gut microbiota and the pathogenesis of MS.[46] MS patients that were included exhibited RRMS phenotype where inflammation played a major role. Samples of healthy controls were used for comparison with MS samples to evaluate differences in the overall microbiota structure and bacterial species that differed between healthy control and MS samples. Faecal samples were obtained every two weeks. *Eggerthella lenta* ($p = .04$) and *Streptococcus thermophilus/salivarius* ($p = .02$) species were increased in comparison with the rest of known species in MS patients.[46] These results suggested that gut microbiota in MS patients was characterized by moderate dysbiosis, highlighting a distinction in the composition of the gut microbiota between patients. Finally, the pathogenesis of MS was associated with the depletion of a large subset of clostridial butyrate.[46] Similarly, in another study, 60 MS patients and 43 healthy controls with comparable demographic characteristics were compared. All MS patients had RR disease but none had an active relapse at the time of study enrolment. The most abundant species at the phylum level were *Euryarchaeota sp* and *Verrucomicrobia sp* compared with controls ($p < .05$).[47] However, when the relative abundances at the genus level were investigated, an increase of *Methanobrevibacter* (a genus in the phylum

Table 3. Studies associating MS and microbiota.

Sample	Bacterial species in MS	Results	References
20 MS 58 HC	Increase of *Eggerthela lenta* and *Streptococcus thermophilus/salivarius* in MS patients	Moderate dysbiosis in MS patients.	[46]
60 MS 43 HC	The most abundant species at the phylum level were *Euryarchaeota sp* and *Verrucomicrobia sp*. Higher abundance at genus levels of *Methanobrevibacter sp* and *Akkermansia sp* was also observed.	Proinflammatory features of these bacteria might be related to its ability to degrade mucus, leading to the breakdown of gut barrier and increased exposure of resident immune cells to microbial antigens.	[47]
31 MS 36 HC	Higher abundance of *Pedobacter sp, Flavobacterium sp, Blautia sp, Dorea sp, Pseudomonas sp* and *Mycoplana sp* in patients with remission state.	Different microbiota structure between MS patients and healthy control groups.	[48]
19 MS	Reduced *Prevotella sp* in RRMS	Increased Th 17 cells in evidenced disease activity patients. Brain autoimmunity was associated with intestinal expansion of Th 17 cells.	[49]
98 MS 120 HC	Greater abundance of *Clostridium cluster IV, Methanobrevibacter sp, Olsenella sp* and *Sporobacter sp* in MS	Different microbiota between MS patients and healthy controls.	[50]

Abbreviations: HC: Healthy Controls; MS: Multiple Sclerosis; Th: *T*-helper lymphocytes.

Euryarchaeota) and *Akkermansia* (a genus in the phylum *Verrucomicrobia*) was found in MS patients when compared with controls ($p < .05$). Interestingly, the archaeon *Methanobrevibacter* had been previously associated with inflammation by its capacity to recruit inflammatory cells and activate human dendritic cells. On the other hand, *Akkermansia* was reported to have regulatory and inflammatory properties. In addition, it transforms mucin to SCFA, mediating immunoregulatory effects.[47] These pro-inflammatory properties might be related to its ability to degrade mucus, which finally breaks the gut barrier increasing microbial antigens exposure on resident immune cells.

Confirming the increase of several genera in MS patients, another study including 31 MS patients and 36 healthy controls, found that the microbiota structure differed significantly between RRMS patients, in both remission and active state, and healthy controls ($p < .001$).[48] In addition, it was shown that the heterogeneity in MS remission group resulted in more variability than in the entire RRMS group as well as in the control group ($p < .001$).[48] In this study, an increased abundance of *Pseudomonas sp, Mycoplana sp, Haemophilus sp, Blautia sp* and *Dorea sp* was observed in MS patients; whereas a decreased abundance of *Parabacteroides sp, Adlercreutzia sp* and *Prevotella sp* was also found.[48] Thus, this study is consistent with the hypothesis that MS patients have gut microbial dysbiosis and exerts an important role during disease exacerbation.

More recently, in another study, small intestinal tissue and peripheral blood samples were collected from 19 MS patients.[49] Total lymphocytes were isolated from the samples. All samples enrolled in this study had a diagnosis of RRMS and were receiving immunomodulatory drugs treatment. They were classified into two subgroups according to the presence or absence of disease activity at a 2 year follow-up: patients with no evidence of disease activity ($n = 9$) and patients with evidence of disease activity ($n = 10$).[49] An increased in Th17 cells was observed in evidence disease activity patients compared with no evidence disease activity patients ($p < .05$). In addition, Th17 cells were negatively associated with the abundance of *Prevotella sp* in evidence of disease activity patients ($p < .01$). This genus produced propionate, an anti-inflammatory metabolite that limited the intestinal expansion of Th17 cell in mice. These data confirmed that brain autoimmunity was also associated with intestinal expansion of Th17 cells (the gut environment enhances pathogenicity of self-reactive T cells by driving them toward a Th17-phenotype) and that reduced *Prevotella* representation in RRMS was related with Th17 cell expansion and disease activity.[49]

In a bigger study including 98 MS patients and 120 healthy controls, a greater abundance of *Clostridium cluster IV* ($p < .001$), *Methanobrevibacter sp* ($p = .037$), *Olsenella sp* ($p = .049$) and *Sporobacter sp* ($p < .001$) in MS patients was observed; whereas a higher abundance of *Butyricicoccus sp* ($p = .007$), *Gemmiger sp* ($p < .001$) and *Intestinibacter sp* ($p = .029$) was found in healthy controls.[50] However, no significant differences were found when the α-diversity was analyzed.

This way, differing results have been reported among studies of gut microbiota in MS patients. Although it cannot be confirmed if total diversity is increased or decreased in MS patients when compared with controls, it can be said that genera microbial populations are clearly different between healthy controls and MS patients. The gut microbiome is affected by various endogenous and exogenous factors including genetic background, age, gender, body mass index and dietary habits, among others, and therefore, further studies with large cohorts and longitudinal collection of samples would aid to understand the relationship between gut microbiota and MS.

Nutritional interventions, microbiota and MS treatment

Gut microbiota affects the development and regulation of the immune system and can be positively modified by diet, suggesting new therapeutic avenues for an inflammatory disease such as MS. There are several studies confirming this hypothesis (Table 4). In one study developed in Norway with a cohort of 152 MS patients and 402 population controls, the risk of presenting MS was tested in children and adolescents in relation with sunlight exposure or vitamin D-related dietary factors. It was found that the increased outdoor activities in the summer were associated with a decreased risk of MS in patients by the age of 16–20 ($p = .001$) and 6–10 ($p = .025$). Additionally, an elevated consumption

Table 4. Studies associating MS and nutritional treatment.

Samples	Nutritional intervention	Results	References
152 MS patients 402 controls	Retrospective recall questionnaire of outdoor activities.	Higher sun exposure was associated with a decreased risk of MS in patients by the age of 16–20 ($p = .001$) and 6–10 ($p = .025$)	[51]
26 RRMS patients 24 HC	Cross-sectional study measuring serum vitamin D levels.	Mean serum vitamin D level was lower in MS patients ($p = .044$).	[52]
2303 MS patients	Questionnaire about type of MS, quality of life, frequency of fish consumption, omega-3 supplementation, disability and disease activity.	Fish consumption >3 times/week increase quality of life, physical and mental health ($p < .001$). Taking 1–20 ml/day of omega-3 led to improve quality of life ($p < .001$).	[53]
113 MS vs 113 healthy women	Food Frequency Questionnaire about nutrients intake in the form of food of groups	Protective role of fruit ($p = .03$) and low-fat dairy ($p = .04$) against MS.	[54]
6989 MS patients	Participants in the NARCOMS Registry completed a dietary screener questionnaire	Higher intake of whole grains was associated with a decreased in MS related disability ($p = .02$).	[55]
100 MS patients	Half of patients were allocated into an anti-inflammatory diet and the other half were allocated into a control diet.	The anti-inflammatory diet improves quality of life in MS patients ($p < .05$).	[17]
20 MS patients	Patients were enrolled into KMAD diet, which offered a restriction of carbohydrates to <20 g per day encouraging greater fat intake.	The short-term KMAD diet improves fatigue ($p = .002$) and depression ($p = .003$) symptoms in MS patients.	[57]

Abbreviations: HC: Healthy Controls; KMAD: Ketogenic Modified Atkins Diet; MS: Multiple Sclerosis; NARCOMS: North American Research Committee of MS; RRMS: Relapsing-Remitting Multiple Sclerosis.

of fish per week (three or more times) was also associated with reduced risk of MS ($p = .024$).[51] In addition, in a cross-sectional study conducted on 26 patients with RRMS and 24 healthy controls, the mean serum vitamin D level was significantly lower in MS patients than in controls ($p = .044$).[52] It is important to mention that the active form of vitamin D can inhibit the expression of IL-2 and INF-y, modulates differentiation of Th17 cells, and also has a role in the balance of Th17/T regulatory cells,[52] thus supporting the previously observed anti-inflammatory role of vitamin D.

In a bigger study, performed with 2303 MS participants, quality of life, disease activity and disability were investigated.[53] It was finally found that consumption of fish more than 3 times a week could increase quality of life, physical and mental health ($p < .001$, for all of them). In addition, taking 1–20 ml/day of omega-3 led to improve health related quality of life ($p < .001$).[53] In another study, 113 MS women patients and 113 healthy women showed a protective role of fruit ($p = .03$) and low-fat dairy ($p = .04$) against MS.[54] Specifically, fruit might be consumed more than five times per week.

In another study performed with 6989 MS patients, it was found that whole grains (fibre source) could be beneficial for MS because a significant association was obtained between higher intake of whole grains and a decrease in MS-related disability ($p = .02$).[55] In another cohort study of 469 MS patients, obesity increased the risk of brain volume loss once MS was developed ($p = .001$).[56]

In a more recent cross-sectional study, 100 MS patients were allocated into an anti-inflammatory (50 patients) and control (50 patients) diet.[17] The anti-inflammatory diet was composed approximately by 55% from carbohydrates, 15% from proteins and 30% from fats. Abundant amounts of vegetables and fruits were included in the diet. White rice was substitute by brown rice, white bread by whole wheat bread and high fat dairy products with probiotic low-fat dairy products. Healthy fats (extra-virgin olive oil and canola) were also included. Spices were recommended instead of salt. White or green tea and moderate amounts of dark chocolate were recommended as well. The consumption of lean read meat and eggs were limited two times a week while lean poultry and fish were the main protein source. Refined carbohydrates and sucrose-containing products, processed food, fast food, fried food and animal fat were not recommended. The study findings indicated a significant improvement in modified fatigue impact scale (MFIS; $p < .001$), physical health

composite (PHC; $p = .015$), mental health composite (MHC; $p = .002$) and an increase in serum IL-4 levels ($p = .033$) in the anti-inflammatory diet group compared to the control group, improving quality of life in MS patients.[17]

Previously, 20 MS patients were enrolled into a 6 month, single-arm, uncontrolled, open-label pilot study examining the feasibility, safety, tolerability and efficacy of a ketogenic modified Atkins diet (KMAD).[57] The KMAD is a type of ketogenic diet which restricts carbohydrates to <20 g per day. This fact combined with higher fat intake developed a ketogenic state. The study showed an improvement in fatigue ($p = .002$) and depression ($p = .003$) over a 3- to 6-month period.[57] These data support the short-term safety of this diet for patients with MS in terms of clinical measurement.

On the other hand, probiotics, prebiotics and FMT have been also used to improve both, digestive and neurological symptoms in MS patients (Table 5). Regarding probiotics, in a 12-week randomized, double-blind and placebo controlled trial, 54 MS patients were requested to consume a probiotic capsule or placebo every two weeks (27 patients with probiotic, 27 patients with placebo).[58] In the intervention group, they received a probiotic capsule daily for 12 weeks which contain *Lactobacillus acidophilus, Lactobacillus casei, Bifidobacterium bifidum and Lactobacillus fermentum*. The subjects in the placebo group received only starch. Probiotic group patients showed favourable effects at the expanded disability status scale ($p = .001$), parameters of mental health ($p < .001$), markers of insulin resistance ($p < .001$) and inflammatory factors ($p < .001$).[55] Therefore, probiotics might be useful to overcome and shorten the duration of neurological symptoms during relapses due to their anti-inflammatory and anti-oxidative actions and their effects on glycaemic control.

Table 5. Studies associating MS with probiotics, prebiotics and FMT.

Samples	Nutritional intervention	Results	References
54 MS patients	Patients received a probiotic capsule daily for 12 weeks containing *L. acidophilus, L. casei, B. bifidum* and *L. fermentum*	Patients expanded disability status scale, parameters of mental health, markers of insulin resistance and inflammatory factors ($p < .001$ for all of them)	[58]
Meta-analysis	Study the effects of probiotics on disease progression, depression, and general health in RRMS patients	EDSS, BDI-II GHQ were improved following probiotics supplementation ($p < .001$, for all of them)	[59]
Meta-analysis	Analyze the efficacy of probiotics in MS treatment based on Bradford Hill criteria	Several treatments using a mixture of probiotics or single-strain probiotics improved MS patients.	[60]
C57Bl/6 mice	Confirm the effect LCFAs and SCFAs in an inflammatory environment	LA promoted polarization of naive T cells toward a Th1 and Th17 differentiation and impaired their intestinal sequestration via the p38-MAPK signaling pathway. PA increased differentiation and proliferation of Tregs.	[61]
268 therapy-naive MS patients and 68 healthy controls	Administration of 1000 mg/day of PA in MS patients.	PA supplementation led to a significant increase of Treg numbers in MS patients and healthy controls ($p < .001$)	[62]
3 MS patients subjected to FMT	Between 5 and 10 FMT infusions depending on the patient.	Constipations and other digestive problems were resolved and MS neurological symptoms improved in all of them.	[63]
61 years old woman with RRMS and 7 relapses in 3 years	A single FMT from her partner via rectal enema.	Her EDSS increased from 2.0 at baseline to 6.0 and was stabilized or minimally increased for 10 years after FMT	[64]
48-year-old Caucasian male with active RRMS for 2 years	1 year of study and 2 FMT transfusions.	A significant and sustained increase in serum BDNF levels was observed. Moreover, the subject's walking and balance metrics were enhanced after FMTs, and significantly improved over the course of the study	[65]

Abbreviations: BDI-II: Beck Depression Inventory-II; BDNF: Brain-derived neurotrophic factor; EDSS: Expanded Disability Status Scale; FMT: Fecal microbiota transplantation; GHQ: General Health Questionnaire; LA: Lauric acid; LCFAs: Long-chain fatty acids; PA: Propionic acid; RRMS: Relapsing remitting MS.

A very recent systematic review and meta-analysis investigated the effects of probiotics on disease progression, depression, general health and anthropometric measurements in RRMS patients.[59] It was found that Expanded Disability Status Scale (EDSS), Beck Depression Inventory-II (BDI-II) and General Health Questionnaire (GHQ) were improved following probiotics supplementation ($p < .001$, for all of them). Another meta-analysis also analyzed the efficacy of probiotics in MS treatment based on Bradford Hill criteria (BHC) as a multiparameter assessment rubric.[60] One probiotic treatment approach emerged as the most strongly supported (BHC score = 9), namely the VSL#3 multi-species formulation, which was assessed in two human and three animal studies. This formulation was composed by *L. paracasei* DSM 24734, *L. plantarum* DSM 24730, *L. acidophilus* DSM 24735, *L. delbrueckii ssp. bulgaricus* DSM 24734, *B. longum* DSM 24736, *B. infantis* DSM 24737, *B. breve* DSM 24732 and *S. thermophilus* DSM 24731. Another promising multispecies formulation with high BHC scores included the Lacto-mix composed by *L. plantarum* DSM 15312, *L. plantarum* DSM 15313, *L. paracasei* DSM 13434 and the combination therapy of *L. crispatus* and *L. rhamnosus*, all of them with a BHC score of 6. On the other hand, therapies based on single-strain probiotics, such as *B. animalis, L. paracasei* and *E. coli* Nissle 1917, received a BHC score of 7.[60]

Regarding prebiotics, a study preformed in mice with a high fat diet to create an inflammatory environment, showed that long-chain fatty acids (LCFAs) such as lauric acid, promote polarization of naive T cells toward a Th1 and Th17 differentiation and impaired their intestinal sequestration via the p38-MAPK signaling pathway. Additionally, mice treated with SCFAs, such as propionic acid (PA), displayed increased differentiation and proliferation of Tregs, and an accompanying resolution of neurological pathology.[61] The decrease of PA levels in MS patients was previously observed, particularly early after disease manifestation. The immunomodulatory effect of PA was confirmed in a study with a cohort of 268 therapy-naive MS patients and 68 healthy controls.[62] In the beginning of the study, PA was significantly reduced in MS patients' serum and fecal samples when compared with healthy controls ($p < .001$, for both of them). The optimal dose of PA was obtained after a titration method and was established in 1000 mg/day. Interestingly, PA supplementation led to a significant increase of Treg numbers in MS patients and healthy controls after 14 days, which persisted throughout long-term supplementation ($p < .001$, for both of them).[62] All these data suggest that that rationally modifying the gut microbiota through diet, in order to promote the growth and maintenance of SCFA producing bacterial, represents a potential strategy for treating MS.

As far as we know, the therapeutic effects of FMT in MS have been reported in only a few studies so far.[63–65] In one of them, three patients were treated with FMT.[63] After 15 years post-FMT, constipations were resolved and MS neurological symptoms improved in all of them. Remarkably, one of these patients (male, 30 years old) required a wheelchair and an indwelling urinary catheter. After five FMT infusions, his constipation was completely resolved. Interestingly his MS also progressively improved, regaining the ability to walk and facilitating the removal of his catheter. Similarly, another patient (male, 29 years old) reported severe constipation, paraesthesia and leg muscle weakness. After 10 days of FMT infusion, the constipation was solved and the patient regained the ability to walk following slow resolution of leg paraesthesia. The third patient (female, 80 years old) was diagnosed of severe constipation and atypical MS with severe muscular weakness resulting in difficulty walking. After 5 FMT infusions, bowel symptoms disappeared and she could walk long distances unassisted.[63] More recently, a 61-year-old woman with RRMS and 7 relapses in 3 years was also treated with FMT.[64] Her Expanded Disability Status Scale (EDSS) increased from 2.0 at baseline to 6.0 and was stabilized or minimally increased for 10 years after FMT. A very recent study was carried out in a 48-year-old Caucasian male with active RRMS for 2 years, and complaints of difficulty in walking and bloating.[65] After 1 year of study and 2 FMT transfusions, a significant and sustained increase in serum BDNF levels was observed. BDNF is normally decreased in MS patients and it is important for neuronal development and for keeping neurons healthy, functioning and growing. The objective measures showed that the subject's walking and balance metrics were

enhanced after FMTs, and significantly improved over the course of the study.[65] These observations confirm that FMT has the potential to provide long-term benefits for MS patients; however, novel clinical trials are required to guide the future use of FMT by evaluating its effectiveness, safety profile, and mechanism of action.

Conclusions and future perspectives

In conclusion, the inflammatory state plays an important role in MS and an anti-inflammatory diet could reduce MS risk. In addition, gut dysbiosis appears in MS patients but more studies are needed to elucidate their role in the pathogenesis of the disease. Thus, nutritional treatment could be an interesting way to improve quality of life in MS patients through the consumption of an anti-inflammatory diet.

Large, better quality, randomized controlled trials are needed to investigate the impact of diet on the pathogenesis of MS. In addition, further investigations about the impact of diet quality on MS symptoms are needed, including intervention studies and longitudinal observational studies that include clinical outcomes and nutrition data. This way, studies with longer follow-up periods are needed to confirm the beneficial clinical effects of the anti-inflammatory diet in MS patients.

Regarding microbiota, gut dysbiosis has been directly associated with a wide range of neurodegenerative diseases. Gut microbes directly modulate intestinal and systemic immune homeostasis to affect neuroinflammation and might contribute to low grade systemic inflammation in these diseases. The possibility of correcting gut dysbiosis by microbiota-based interventions represents an interesting approach in preventing and treating human pathologies. In this review, several studies have shown that both, microbiota modifications and nutritional interventions increased quality of life, physical and mental health, improved fatigue, depression and decreased disability in MS patients. Thus, the consumption of anti-inflammatory diets and the intake of pro/prebiotics and FMT infusions can be of paramount importance as they can relief and shorten neurological symptoms and improve mental and physical health in MS patients.

Acknowledgement

Dr. Orenes-Piñero is supported by a postdoctoral contract from the Instituto Murciano de Investigaciones Biosanitarias Virgen de la Arrixaca (IMIB-Arrixaca, Murcia, Spain).

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

The author(s) reported there is no funding associated with the work featured in this article.

ORCID

Esteban Orenes-Piñero http://orcid.org/0000-0003-3979-6678

References

[1] Larroya-García, A.; Navas-Carrillo, D.; Orenes-Piñero, E. Impact of Gut Microbiota on Neurological Diseases: Diet Composition and Novel Treatments. *Crit. Rev. Food Sci. Nutr.* 2019, *59*(19), 3102–3116. DOI: 10.1080/10408398.2018.1484340.

[2] Noor, F.; Kaysen, A.; Wilmes, P.; Schneider, J. G. The Gut Microbiota and Hematopoietic Stem Cell Transplantation: Challenges and Potentials. *J. Innate. Immun*. 2019, *11*(5), 405—415. DOI: 10.1159/000492943.
[3] Illiano, P.; Brambilla, R.; Parolini, C. The Mutual Interplay of Gut Microbiota, Diet and Human Disease. *Febs. J*. 2020, *287*(5), 833—855. DOI: 10.1111/febs.15217.
[4] Attaye, I.; Pinto-Sietsma, S. J.; Herrema, H.; Nieuwdorp, M. A Crucial Role for Diet in the Relationship Between Gut Microbiota and Cardiometabolic Disease. *Annu. Rev. Med*. 2020, *71*, 149—161. DOI: 10.1146/annurev-med-062218-023720.
[5] Kazemian, N.; Mahmoudi, M.; Halperin, F.; Wu, J. C.; Pakpour, S. Gut Microbiota and Cardiovascular Disease: Opportunities and Challenges. *Microbiome*. 2020, *8*(1), 36. DOI: 10.1186/s40168-020-00821-0.
[6] Gubert, C.; Kong, G.; Renoir, T.; Hannan, A. J. Exercise, Diet and Stress as Modulators of Gut Microbiota: Implications for Neurodegenerative Diseases. *Neurobiol. Dis*. 2020, *134*, 104621. DOI: 10.1016/j.nbd.2019.104621.
[7] Crovesy, L.; Masterson, D.; Lopes-Rosado, E. Profile of the Gut Microbiota of Adults with Obesity: A Systematic Review. *Eur. J. Clin. Nutr*. 2020, *74*(9), 1251—1262. DOI: 10.1038/s41430-020-0607-6.
[8] Jiao, Y.; Wu, L.; Huntington, N. D.; Zhang, X. Crosstalk Between Gut Microbiota an Innate Immunity and Its Implication in Autoimmune Diseases. *Front. Immunol*. 2020, *11*, 282. DOI: 10.3389/fimmu.2020.00282.
[9] Fengjiao, L.; Zhang, T.; He, Y.; Gu, W.; Yang, X.; Zhao, R.; Yu, J. Inflammation Inhibition and Gut Microbiota Regulation by TSG to Combat Atherosclerosis in ApoE -/- Mice. *J. Ethnopharmacol*. 2020, *247*, 112232. DOI: 10.1016/j.jep.2019.112232.
[10] Amoroso, C.; Perillo, F.; Strati, F.; Fantini, M. C.; Caprioli, F.; Facciotti, F. The Role of Gut Microbiota Biomodulators on Mucosal Immunity and Intestinal Inflammation. *Cells*. 2020, *9*(5), 1234. DOI: 10.3390/cells9051234.
[11] Paul, A.; Comabella, M.; Gandhi, R. Biomarkers in Multiple Sclerosis. *Cold Spring Harb. Perspect. Med*. 2019, *9*(3), a029058. DOI: 10.1101/cshperspect.a029058.
[12] Lassmann, H. Pathogenic Mechanisms Associated with Different Clinical Courses of Multiple Sclerosis. *Front. Immunol*. 2019, *9*, 311. DOI: 10.3389/fimmu.2018.03116.
[13] Chenard, C. A.; Rubenstein, L. M.; Snetselaar, L. G.; Wahls, T. L. Nutrient Composition Comparison Between the Low Saturated Fat Swank Diet for Multiple Sclerosis and Healthy U.S.-Style Eating Pattern. *Nutrients*. 2019, *11*(3), 616. DOI: 10.3390/nu11030616.
[14] Pegoretti, V.; Swanson, K. A.; Bethea, J. R.; Probert, L.; Eisel, U. L. M.; Fischer, R. Inflammation and Oxidative Stress in Multiple Sclerosis: Consequences for Therapy Development. *Oxid. Med. Cell Longev*. 2020, 7191080. DOI: 10.1155/2020/7191080.
[15] Macaron, G.; Ontaneda, O. Diagnosis and Management of Progressive Multiple Sclerosis. *Biomedicines*. 2019, *7*(3), 56. DOI: 10.3390/biomedicines7030056.
[16] Schepici, G.; Silvestro, S.; Bramanti, P.; Mazzon, E. The Gut Microbiota in Multiple Sclerosis: An Overview of Clinical Trials. *Cell Transplant*. 2019, *28*(12), 1507—1527. DOI: 10.1177/0963689719873890.
[17] Mousavi-Shirazi-Fard, Z.; Mazloom, Z.; Izadi, S.; Fararouei, M. The Effects of Modified Anti-Inflammatory Diet on Fatigue, Quality of Life, and Inflammatory Biomarkers in Relapsing-Remitting Multiple Sclerosis Patients: A Randomized Clinical Trial. *Int. J. Neurosci*. 2020, 1—9. DOI: 10.1080/00207454.2020.1750398.
[18] Sato, W.; Yamamura, T. Multiple Sclerosis: Possibility of a Gut Environment-Induced Disease. *Neurochem. Int*. 2019, *130*, 104475. DOI: 10.1016/j.neuint.2019.104475.
[19] Miyake, S.; Yamamura, T. Gut Environmental Factors and Multiple Sclerosis. *J. Neuroimmunol*. 2019, *329*, 20—23. DOI: 10.1016/j.jneuroim.2018.07.015.
[20] Lorenzo, D.; GianVicenzo, Z.; Luca, R. C.; Karan, G.; Jorge, V.; Roberto, M.; Javad, P. Oral-Gut Microbiota and Arthritis: Is There an Evidence-Based Axis? *J. Clin. Med*. 2019, *8*(10), 0. DOI: 10.3390/jcm8101753.
[21] AlAmmar, W.; Albeesh, F. H.; Ibrahim, L. M.; Algindan, Y. Y.; Yamani, L. Z.; Khattab, R. Y. Effect of Omega-3 Fatty Acids and Fish Oil Supplementation on Multiple Sclerosis: A Systematic Review. *Nutr. Neurosci*. 2019, 1–11. DOI: 10.1080/1028415X.2019.1659560.
[22] Sanchez, J. M. S.; DePaula-Silva, A. B.; Libbey, J. E.; Fujinami, R. S. Role of Diet in Regulating the Gut Microbiota and Multiple Sclerosis. *Clin. Immunol*. 2020, 108379. DOI: 10.1016/j.clim.2020.108379.
[23] Li, J. W.; Fang, B.; Pang, G. F.; Zhang, M.; Ren, F. Z. Age-And Diet-Specific Effects of Chronic Exposure to Chlorpyrifos on Hormones, Inflammation and Gut Microbiota in Rats. *Pestic. Biochem. Physiol*. 2019, *159*, 68—79. DOI: 10.1016/j.pestbp.2019.05.018.
[24] Levy, M.; Kolodziejczyk, A. A.; Thaiss, C. A.; Elinav, E. Dysbiosis and the Immune System. *Nat. Rev. Immunol*. 2017, *17*(4), 219–232. DOI: 10.1038/nri.2017.7.
[25] Nourbakhsh, B.; Mowry, E. M. Multiple Sclerosis Risk Factors and Pathogenesis. *Continuum (Minneap Minn)*. 2019, *25*(3), 596—610. DOI: 10.1212/CON.0000000000000725.
[26] Bruno, A.; Dolcetti, E.; Rizzo, F. R.; Fresegna, D.; Musella, A.; Gentile, A.; De Vito, F.; Caioli, S.; Guadalupi, L.; Bullita, S., et al. Inflammation-Associated Synaptic Alterations as Shared Threads in Depression and Multiple Sclerosis. *Front. Cell. Neurosci.*, 2020, *14*, 169. DOI: 10.3389/fncel.2020.00169.

[27] Dobson, R.; Giovannoni, G. Multiple Sclerosis: A Review. *Eur. J. Neurol.* 2019, *26*(1), 27—40. DOI: 10.1111/ene.13819.
[28] Matthews, P. M. Chronic Inflammation in Multiple Sclerosis – Seeing What Was Always There. *Nat. Rev. Neurol.* 2019, *15*(10), 582—593. DOI: 10.1038/s41582-019-0240-y.
[29] Michaliková, D.; Síma, M.; Slanar, O. New Insights in the Mechanisms of Impaired Redox Signaling and Its Interplay with Inflammation and Immunity in Multiple Sclerosis. *Physiol. Res.* 2020, *69*(1), 1—19. DOI: 10.33549/physiolres.934276.
[30] Ruiz, F.; Vigne, S.; Pot, C. Resolution of Inflammation During Multiple Sclerosis. *Semin. Immunopathol.* 2019, *41*(6), 711—726. DOI: 10.1007/s00281-019-00765-0.
[31] Boziki, M. K.; Kesidou, E.; Theotokis, P.; Mentis, A. A.; Karafoulidou, E.; Melnikov, M.; Siridova, A.; Rogovski, V.; Boyko, A.; Grigoriadis, N. Microbiome in Multiple Sclerosis; Where are We, What We Know and Do Not Know. *Brain Sci.* 2020, *10*(4), 234. DOI: 10.3390/brainsci10040234.
[32] Cryan, J. F.; O'-Riordan, K. J.; Sandhu, K.; Peterson, V.; Dinan, T. G. The Gut Microbiome in Neurological Disorders. *Lancet. Neurol.* 2020, *19*(2), 179—194. DOI: 10.1016/S1474-4422(19)30356-4.
[33] Xu, H.; Wang, X.; Feng, W.; Liu, Q.; Zhou, S.; Liu, Q.; Cai, L. The Gut Microbiota and Its Interactions with Cardiovascular Disease. *Microb. Biotechnol.* 2020, *13*(3), 637—656. DOI: 10.1111/1751-7915.13524.
[34] Adak, A.; Khan, M. R. An Insight into Gut Microbiota and Its Functionalities. *Cell. Mol. Life Sci.* 2019, *76*(3), 473—493. DOI: 10.1007/s00018-018-2943-4.
[35] Shankar, V.; Gouda, M.; Moncivaiz, J.; Gordon, A.; Reo, N. V.; Hussein, L.; Paliy, O. Differences in Gut Metabolites and Microbial Composition and Functions Between Egyptian and U.S. Children are Consistent with Their Diets. *mSystems.* 2017, *2*, 1–15. DOI: 10.1128/mSystems.00169-16.
[36] Ramírez-Macías, I.; Orenes-Piñero, E.; Camelo-Castillo, A.; Rivera-Caravaca, J. M.; López-García, C.; Marín, F. Novel Insights in the Relationship of Gut Microbiota and Coronary Artery Diseases. *Crit. Rev. Food Sci. Nutr.* 2021, 1–13. DOI: 10.1080/10408398.2020.1868397.
[37] Grundy, D.; De Giorgio, R.; Schemann, M. Enteric Nervous System: Disorders. *Encycl. Neurosci.* 2009, 1077–1082. DOI: 10.1016/B978-008045046-9.00661-6.
[38] Aggeletopoulou, I.; Konstantakis, C.; Assimakopoulos, S. F.; Triantos, C. The Role of the Gut Microbiota in the Treatment of Inflammatory Bowel Diseases. *Microb. Pathog.* 2019, *137*, 103774. DOI: 10.1016/j.micpath.2019.103774.
[39] Fung, T. C. The Microbiota-Immune Axis as a Central Mediator of Gut-Brain Communication. *Neurobiol. Dis.* 2020, *136*, 10471. DOI: 10.1016/j.nbd.2019.104714.
[40] Davani-Davari, D.; Negahdaripour, M.; Karimzadeh, I.; Seifan, M.; Mohkam, M.; Masoumi, S. J.; Berenjian, A.; Ghasemi, Y. Prebiotics: Definition, Types, Sources, Mechanisms, and Clinical Applications. *Foods.* 2019, *8*(3), 92. DOI: 10.3390/foods8030092.
[41] Jilek, S.; Schluep, M.; Rossetti, A. O.; Guignard, L.; Le Goff, G.; Pantaleo, G.; Du Pasquier, R. A. CSF Enrichment of Highly Differentiated CD8+ T Cells in Early Multiple Sclerosis. *Clin. Immunol.* 2007, *123*(1), 105—113. DOI: 10.1016/j.clim.2006.11.004.
[42] Annibali, V.; Ristori, G.; Angelini, D. F.; Serafini, B.; Mechelli, R.; Cannoni, S.; Romano, S.; Paolillo, A.; Abderrahim, H.; Diamantini, A., et al. Cd161(high)cd8+t Cells Bear Pathogenetic Potential in Multiple Sclerosis. *Brain.*2011, *134*(Pt 2), 542—554. DOI: 10.1093/brain/awq354.
[43] Machado-Santos, J.; Saji, E.; Tröscher, A. R.; Paunovic, M.; Liblau, R.; Gabriely, G.; Bien, C. G.; Bauer, J.; Lassmann, H. The Compartmentalized Inflammatory Response in the Multiple Sclerosis Brain is Composed of Tissue-Resident CD8+ T Lymphocytes and B Cells. *Brain.* 2018, *141*(7), 2066—2082. DOI: 10.1093/brain/awy151.
[44] Kadowaki, A.; Saga, R.; Lin, Y.; Sato, W.; Yamamura, T. Gut Microbiota-Dependent CCR9+CD4+ T Cells are Altered in Secondary Progressive Multiple Sclerosis. *Brain.* 2019, *142*(4), 916—931. DOI: 10.1093/brain/awz012.
[45] Abdollahpour, I.; Jakimovski, D.; Shivappa, N.; Hébert, J. R.; Vahid, F.; Nedjat, S.; Mansournia, M. A.; Weinstock-Guttman, B. Dietary Inflammatory Index and Risk of Multiple Sclerosis: Findings from a Large Population-Based Incident Case-Control Study. *Clin. Nutr.* 2020, *39*(11), 3402–3407. DOI: 10.1016/j.clnu.2020.02.033.
[46] Miyake, S.; Kim, S.; Suda, W.; Oshima, K.; Nakamura, M.; Matsuoka, T.; Chihara, N.; Tomita, A.; Sato, W.; Kim, S. W., et al. Dysbiosis in the Gut Microbiota of Patients with Multiple Sclerosis, with Striking Depletion of Species Belonging to Clostridia Xiva and IV Clusters. *PLoS One*, 2015, *10*, e0137429. DOI: 10.1371/journal.pone.0137429.
[47] Jangi, S.; Gandhi, R.; Cox, L. M.; Li, N.; von Glehn, F.; Yan, R.; Patel, B.; Mazzola, M. A.; Liu, S.; Glanz, B. L., et al. Alterations of the Human Gut Microbiome in Multiple Sclerosis. *Nat. Commun.*2016, *7*(9), 12015. DOI: 10.1038/ncomms12015.
[48] Chen, J.; Chia, N.; Kalari, K. R.; Yao, J. Z.; Novotna, M.; Paz-Soldan, M. M.; Luckey, D. H.; Marietta, E. V.; Jeraldo, P. R.; Chen, X., et al. Multiple Sclerosis Patients Have a Distinct Gut Microbiota Compared to Healthy Controls. *Sci. Rep.*, 2016, *6*, 28484. DOI: 10.1038/srep28484.
[49] Cosorich, I.; Dalla-Costa, G.; Sorini, C.; Ferrarese, R.; Messina, M. J.; Dolpady, J.; Radice, E.; Mariani, A.; Testoni, P. A.; Caducci, F., et al. High Frequency of Intestinal Th17 Cells Correlates with Microbiota Alterations and Disease Activity in Multiple Sclerosis. *Sci. Adv.*2017, *3*(7), e1700492. DOI: 10.1126/sciadv.1700492.

[50] Reynders, T.; Devolder, L.; Valles-Colomer, M.; Van Remoortel, A.; Joossens, M.; De Keyser, J.; Nagels, G.; D´-Hooghe, M.; Raes, J. Gut Microbiome Variation is Associated to Multiple Sclerosis Phenotypic Subtypes. *Ann. Clin. Transl. Neurol.* 2020, *7*(4), 406—419. DOI: 10.1002/acn3.51004.

[51] Kampman, M. T.; Wilsgaard, T.; Mellgren, S. I. Outdoor Activities and Diet in Childhood and Adolescence Relate to MS Risk Above the Arctic Circle. *J. Neurol.* 2007, *254*(4), 471—477. DOI: 10.1007/s00415-006-0395-5.

[52] Aktürk, T.; Turan, Y.; Tanik, N.; Karadağ, M. E.; Sacmaci, H.; Inan, L. E. Vitamin D, Vitamin D Binding Protein, Vitamin D Receptor Levels and Cardiac Dysautonomia in Patients with Multiple Sclerosis: A Cross-Sectional Study. *Arq. Neuropsiquiatr.* 2019, *77*(12), 848—854. DOI: 10.1590/0004-282X20190182.

[53] Jelinek, G. A.; Hadgkiss, E. J.; Weiland, T. J.; Pereira, N. G.; Marck, C. H.; van der Meer, D. M. Association of Fish Consumption and Omega-3 Supplementation with Quality of Life, Disability and Disease Activity in an International Cohort of People with Multiple Sclerosis. *Int. J. Neurosci.* 2013, *123*(11), 792—800. DOI: 10.3109/00207454.2013.803104.

[54] Bagheri, M.; Maghsoudi, Z.; Fayazi, S.; Elahi, N.; Tabesh, H.; Majdinasab, N. Several Food Items and Multiple Sclerosis: A Case-Control Study in Ahvaz (Iran). *Iran J. Nurs. Midwiferi. Res.* 2014, *19*(6), 659—665.

[55] Fitzgerald, K. C.; Tyry, T.; Salter, A.; Cofield, S. S.; Cutter, G.; Fox, R.; Marrie, R. A. Diet Quality is Associated with Disability and Symptom Severity in Multiple Sclerosis. *Neurology*. 2018, *90*(1), e1—e11. DOI: 10.1212/WNL.0000000000004768.

[56] Mowry, E. M.; Azevedo, C. J.; McCulloch, C. E.; Okuda, D. T.; Lincoln, R. R.; Waubant, E.; Hauser, S. L.; Pelletier, D. Body Mass Index, but Not Vitamin D Status, is Associated with Brain Volume Change in MS. *Neurology*. 2018, *91*(24), e2256—e2264. DOI: 10.1212/WNL.0000000000006644.

[57] Brenton, J. N.; Banwell, B.; Bergqvist, A. G. C.; Lehner-Gulotta, D.; Gampper, L.; Leytham, E.; Coleman, R.; Goldman, M. D. Pilot Study of a Ketogenic Diet in Relapsing-Remitting MS. *Neurol. Neuroimmunol. Neuroinflamm*. 2019, *6*(4), e565. DOI: 10.1212/NXI.0000000000000565.

[58] Kouchaki, E.; Tamtaji, O. R.; Salami, M.; Bahmani, F.; Daneshvar Kakhaki, R.; Akbari, E.; Tajabadi-Ebrahimi, M.; Jafari, P.; Asemi, Z. Clinical and Metabolic Response to Probiotic Supplementation in Patients with Multiple Sclerosis: A Randomized, Double-Blind, Placebo-Controlled Trial. *Clin. Nutr.* 2017, *36*(5), 1245—1249. DOI: 10.1016/j.clnu.2016.08.015.

[59] Mirashrafi, S.; Hejazi-Taghanaki, S. Z.; Sarlak, F.; Moravejolahkami, A. R.; Hojjati-Kermani, M. A.; Haratian, M. Effect of Probiotics Supplementation on Disease Progression, Depression, General Health, and Anthropometric Measurements in Relapsing-Remitting Multiple Sclerosis Patients: A Systematic Review and Meta-Analysis of Clinical Trials. *Int. J. Clin. Pract.* 2021, *75*(11), e14724. DOI: 10.1111/ijcp.14724.

[60] Blais, L. L.; Montgomery, T. L.; Amiel, E.; Deming, P.; Krementsov, D. N. Probiotic and Commensal Gut Microbial Therapies in Multiple Sclerosis and Its Animal Models: A Comprehensive Review. *Gut. Microbes*. 2021, *13*(1), 1943289. DOI: 10.1080/19490976.2021.1943289.

[61] Haase, S.; Mäurer, J.; Duscha, A.; Lee, D. H.; Balogh, A.; Gold, R.; Müller, D. N.; Haghikia, A.; Linker, R. A. Propionic Acid Rescues High-Fat Diet Enhanced Immunopathology in Autoimmunity via Effects on Th17 Responses. *Front. Immunol.* 2021, *12*, 701626. DOI: 10.3389/fimmu.2021.701626.

[62] Duscha, A.; Gisevius, B.; Hirschberg, S.; Yissachar, N.; Stangl, G. I.; Eilers, E.; Bader, V.; Haase, S.; Kaisler, J.; David, C., et al. Propionic Acid Shapes the Multiple Sclerosis Disease Course by an Immunomodulatory Mechanism. *Cell*.2020, *180*(6), 1067–1080.e16. DOI: 10.1016/j.cell.2020.02.035.

[63] Borody, T.; Leis, S.; Campbell, J.; Torres, M.; Nowak, A. Fecal Microbiota Transplantation (FMT) in Multiple Sclerosis (MS). *Am. J. Gastroenterol.* 2011, *106*, S942.

[64] Makkawi, S.; Camara-Lemarroy, C.; Metz, L. Fecal Microbiota Transplantation Associated with 10 Years of Stability in a Patient with SPMS. *Neurol. Neuroimmunol. Neuroinflamm*. 2018, *5*(4), e459. DOI: 10.1212/NXI.0000000000000459.

[65] Engen, P. A.; Zaferiou, A.; Rasmussen, H.; Naqib, A.; Green, S. J.; Fogg, L. F.; Forsyth, C. B.; Raeisi, S.; Hamaker, B.; Keshavarzian, A. Single-Arm, Non-Randomized, Time Series, Single-Subject Study of Fecal Microbiota Transplantation in Multiple Sclerosis. *Front. Neurol.* 2020, *11*, 978. DOI: 10.3389/fneur.2020.00978.