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Review

ON POSSIBLE PRACTICAL APPLICATIONS OF THE GUT MICROBIOME RESEARCH IN THE PREVENTION, DIAGNOSIS, ASSESSMENT OF, AND TREATMENT MODIFICATION FOR MULTIPLE SCLEROSIS IN PATIENTS FROM RISK GROUPS

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Research into the gut microbiota (GM) in multiple sclerosis (MS) has the potential to lead to a number of practical applications in the prevention, diagnosis, assessment of, and treatment modification for, MS. Four most promising areas include biomarkers, treatment personalization, drug development as well as disease prevention and mitigation.

Changes in the GM have been observed in individuals with MS; analysis of the GM composition may help to identify individuals at risk of developing the disease or to monitor disease progression. Dietary interventions aimed at improving gut health could be used as a complementary approach to traditional MS treatments in order to reduce inflammation thereby potentially improving MS symptoms and lessening disease progression. Differences in the GM between individuals with MS suggest that personalized treatment approaches based on an individual's microbiome composition could be effective. Manipulating the GM could therefore be a potential avenue for drug development in MS. In addition, the exploration of bacteria or bacterial metabolites as therapeutic agents to modulate the immune system and reduce inflammation is also promising.

Such explorations may even help identify strategies for preventing the development of MS in at-risk individuals. Overall, practical applications of gut microbiome research in MS are still in the early stages and further research is needed to fully understand the mechanisms underlying the relationship between the gut microbiome and MS and to determine the most effective interventions for improving gut health in individuals with the disease.

Keywords: *multiple sclerosis, gut microbiome, prevention, diagnostics, treatment personalization, biomarkers, risk of a disease, diet.*

Research into gut microbiota (GM) in multiple sclerosis (MS) has over time yielded a number of practical directions in research and application of said research when it comes to the prevention, diagnosis, assessment of and treatment modification for MS. Multiple sclerosis (MS) is a demyelinating and neurodegenerative autoimmune disease of the central nervous system (CNS). MS has a mean diagnosis age of 30 and is the most common inflammatory neurological disease in young adults [1]. Since this disease strikes so early and then affects people indefinitely, it is of the utmost importance to be able to not only provide the right treatment, but to also assess the effectiveness of said treatment.

In recent years, there has been increasing interest in the role of the GM in multiple sclerosis and a growing body of research in this area.

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Research into the gut microbiome and multiple sclerosis (MS) is still in its early stages, but there are several possible practical applications of this research in the assessment and treatment modification of MS.

Firstly, analysis of the gut microbiome could potentially be used as a diagnostic tool for MS. Changes in the gut microbiome have been observed in individuals with MS, and analysis of the gut microbiota composition may help to identify individuals at risk of developing the disease or to monitor disease progression.

In 2022, a study published by the IMSMS consortium in *Cell* comprised of a large multi-center study of MS patients and household healthy controls [2]. The study found that gut bacteria in individuals with MS were less diverse than those in healthy individuals, and that specific bacterial species were associated with disease activity and disability. The researchers suggested that changes in the gut microbiome may contribute to the development and progression of MS by promoting inflammation and altering the balance of immune cells.

Secondly, dietary interventions aimed at improving gut health could be used to complement traditional MS treatments since it is known that the GM changes during treatment with drugs [3, 4]. For example, a diet high in fiber and prebiotic and probiotic foods may help restore the balance of beneficial gut bacteria and reduce inflammation thereby potentially improving MS symptoms and slowing down the disease progression.

A *Nutrients* review in 2023 by Kurowska et al. showed that an imbalance in the function as well as composition of the GM is critical in the pathogenesis of neurological diseases [5]. Specifically for MS, dietary intervention as with the Mediterranean or the Ketogenic diets, and consumption of nuts, vegetables, legumes, vitamins, and anti-inflammatories like omega-3 and many others, were associated with improvements. Significant improvements were noted by using the Modified Fatigue Impact Scale (MFIS) and physical and mental components of the Multiple Sclerosis Quality of Life (MSQoL-54) in MS patients. Biomarker-wise, it was also noted that levels of the anti-inflammatory cytokine interleukin 4 (IL-4) increased while levels of serum neurofilament light chain level (sNfL) decreased thus indicating a potential neuroprotective effect with the latter biomarker [6].

In 2022, the article in *Aging and Disease* by Z. Jiang et al. detailed the physiological basis of the ketogenic diet as well as its functions within regulation of neuroinflammation and therefore its protective role in normal brain aging and neurodegenerative diseases [7]. Diseases such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, and Huntington's disease were mentioned by name and it would not be a stretch to include MS toward these same findings.

Another study published in *Frontiers in Neuroscience* in 2022 found that probiotic supplementation can have beneficial effects on serum levels of CRP and IFN-γ, for example, both of which are related to systemic inflammation [8].

All these findings suggest that the gut microbiome may play an important role in the development and progression of MS and that dietary interventions aimed at improving gut health may be a promising avenue toward managing the disease. However, further research is needed to fully understand the mechanisms underlying the relationship between the gut microbiome and MS and to determine the most effective interventions for improving gut health, and hopefully overall outcome, in individuals with the dis-

ease. Potentially, personalized nutritional interventions may constitute a non-invasive and effective strategy in combating neurological disorders [9].

Thirdly, the use of probiotics or fecal microbiota transplantation (FMT) may be explored as a potential treatment for MS. FMT involves transferring fecal material from a healthy donor into the gut of a recipient with the aim to restore a healthy gut microbiome. While FMT is not currently an approved treatment for MS, it has shown promise in small studies and may merit future research.

In 2022, Correale et al. (*Nature reviews, Neurology*) reviewed a number of studies that looked at microbiome alteration in multiple sclerosis across different disease courses including clinically isolated syndrome (CIS), relapsing-remitting MS (RRMS), primary-progressive MS (PPMS) and secondary-progressive MS (SPMS) along with the treatments they used and controls. The authors were able to identify several possible therapeutic strategies aimed at GM alteration: probiotics, FMT, dietary modifications as well as bacterial metabolite supplementation, for example using short-chain fatty acids [10].

The results of K.F. Al et al. in 2022 in MSJ showed that FMT was both safe and well-tolerated among the RRMS patient cohort. There is a potential for it to enhance the microbiota that may be protective against MS. Additionally, there is evidence that FMT could reduce small intestinal permeability, which is often elevated in MS patients [11]. Nonetheless, the authors acknowledged that further research involving larger sample sizes and longer follow-up periods is needed to ascertain whether FMT is a viable therapy for MS [12].

Similarly, in a review by Matherson et al. published in 2023 in the *International Journal of Molecular Science*s, the authors aimed to summarize FMT research in neurodegenerative disease in both human and animal studies [13]. The authors acknowledged that the current state of research on gut microbiome modification through FMT as a potential treatment for diseases like MS is still in its early stages and has several limitations. While case studies and animal studies offer valuable insights for future research, clinical trials are still limited or absent. Moreover, FMT protocols vary greatly among studies and standardized procedures are not yet available making it challenging to draw conclusions on a larger scale. For example, different delivery routes, the use of antibiotics beforehand, and the number of FMT infusions can significantly affect outcomes. To address these limitations, future research should consider establishing standard protocols or examining the impact of the aforementioned factors to facilitate comparison between studies. Despite these limitations, the authors posit that the available evidence suggests that FMT may provide relief from symptoms with minimal side effects and warrants further investigation. This is particularly valuable in the context of limited long-term treatment options for these diseases. Therefore, further research, particularly clinical trials, is eagerly anticipated in this field [13].

Finally, understanding the role of environmental factors in shaping the gut microbiome and their potential impact on MS could inform public health efforts to prevent the disease or modify its progression [5, 14, 15]. For example, public health campaigns aimed at reducing exposure to environmental toxins or promoting a healthy diet and lifestyle could help to improve gut health and potentially reduce the incidence and severity of MS.

In a 2022 review article in *Cureus*, Jayasinghe et al. investigated diet and the

gut microbiome and how they relate to the progression of MS disease course [15]. They found the past decade's research has shown multiple instances of interplay between genetics and environmental factors in the pathogenesis of MS. The functions of the gut-brain axis, antioxidants, vitamins, obesity, and various diets are also covered in this review. Research has found that the gut-brain axis plays a crucial role in regulating the immune response and maintaining immune homeostasis, which is significant in the development of MS [16–18]. Moreover, recent studies suggest that modifications to the gut microbiome through dietary changes can trigger inflammation and demyelination in MS. Concomitantly, in RRMS, adopting the ketogenic diet has resulted in improvements in quality of life, fatigue, and depression [19]. Additionally, adherence to the Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diet has demonstrated a reduction in both MS incidence and cognitive decline. These findings underscore the importance of considering the impact of diet and the gut microbiota in managing patients with MS therapeutically [15].

In order to determine the potential benefits of these approaches on the gut microbiota in individuals with MS, it is necessary to conduct controlled clinical trials with uniform protocols. To ensure the validity of these studies, it is important to enroll large groups of patients who have been carefully phenotyped, including an assessment of their genetic makeup, dietary habits, medication usage, and any coexisting illnesses. These patients should then be compared with carefully selected individuals who do not have the disease. If these studies are properly designed and executed, they may provide insight into whether manipulating the gut microbiota could be a useful addition to the existing MS treatment options [10].

Acquiring this knowledge is crucial not only for understanding the underlying causes of neuroinflammation but also for identifying diagnostic biomarkers and developing novel treatment approaches that target the gut microbiota composition to restore immune cell homeostasis in immune-mediated CNS diseases. Overall, research into the gut microbiome and MS has the potential to inform novel diagnostic and therapeutic strategies, as well as public health interventions aimed at preventing or modifying the disease. Trusting what the gut has to tell us may very well help yield better outcomes.

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