Uncovering the Hidden Link Between the Aberrant Intestinal Microbiome and Fibromyalgia

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Abstract: Fibromyalgia is a multifaceted syndrome primarily characterized by chronic widespread pain and fatigue. Despite its significant prevalence and incidence, the mechanisms mediating the disease pathogenesis have remained poorly understood; however, increasing evidence suggests a potentially central role of intestinal dysbiosis. Researchers have been examining possible diagnostic biomarkers, such as *Helicobacter pylori* infection, urine metabolite profiles, and cytokine levels, which reflect these microbiome changes. Additionally, evaluation of therapeutic interventions targeting the gut microbiome, including probiotics, fecal microbiota transplantation, and antibiotics for specific infections, has highlighted their potential in alleviating fibromyalgia symptoms. This article delves into the emerging role of the gut microbiome in fibromyalgia pathogenesis, illustrating how alterations in gut bacterial composition and diversity are implicated in the pathophysiology of the disease through the gut-brain axis, and sets a direction for future research to enhance diagnostic accuracy and therapeutic efficacy of this complex condition.

Keywords
Fibromyalgia, gut ecosystem, intestinal dysbiosis, pathophysiology, gut-brain axis, microbiome modulation

Fibromyalgia is a medical condition marked by persistent, widespread pain in the musculoskeletal system.[1] This core symptom is often accompanied by fatigue, cognitive impairments, psychiatric issues, and a variety of bodily symptoms.[2] The causes of fibromyalgia remain unclear, and its pathophysiologic mechanisms are not well understood. Notably, there is no indication of tissue inflammation, even though individuals experience pain in soft tissues. Current research points to fibromyalgia being a disorder related to the regulation of pain, falling under the broader category of a central sensitization syndrome.[3] This condition is also understood as a neurosensory disorder, indicating an abnormal processing of pain signals in the brain. Over the recent

Table. Key Findings and Relevance of Research on the Gut Microbiome and Fibromyalgia

Research	Key findings	Relevance of research
Pomares et al[3]	Relationship between multimodal brain imaging and histologic analysis in fibromyalgia	Enhances understanding of neurologic aspects
Wolfe et al[4]; Queiroz[5]	Prevalence, characteristics, and epidemiologic data of fibromyalgia	Provides insights into prevalence and demographic distribution
Galvez-Sánchez and Reyes Del Paso[6]	Evolution of fibromyalgia diagnostic criteria	Highlights advancements in fibromyalgia diagnosis
Duque and Fricchione[8]	Relationship of fibromyalgia as a neuropsychiatric disorder with central pain regulation	Positions fibromyalgia within broader pain syndrome categories
Minerbi et al[11]	Connection between gut microbiome and fibromyalgia	Suggests a role for the gut microbiome in fibromyalgia symptomatology
Blomberg et al[12]	Proposed autoimmune response in ME/CFS and fibromyalgia	Suggests shared pathophysiologic mechanisms with fibromyalgia
Defaye et al[13]	Role of gut microbiota as a pain regulator in chronic pain conditions	Indicates potential microbiome targets for fibromyalgia treatment
Erdrich et al[14]	Microbiome dysbiosis as biomarker in fibromyalgia	Supports the use of microbiome profiles for fibromyalgia diagnosis
Michalsen et al[15]; Pimentel et al[16]	Influence of the gut microflora on fibromyalgia	Reinforces the gut-brain axis in fibromyalgia
Akkaya et al[17]; Olama and El-Arman[18]	Seropositivity and higher prevalence of *Helicobacter pylori* in fibromyalgia patients	Suggests a potential role of *H pylori* in fibromyalgia
Malatji et al[21]	Increased urine metabolite levels linked to metabolic dysregulation in fibromyalgia	Points to metabolic biomarkers for fibromyalgia diagnosis
Malatji et al[22]	GC-MS metabolomics, metabolic dysregulation, and intestinal dysbiosis in fibromyalgia	Supports metabolic and microbiome involvement in fibromyalgia
Clos-Garcia et al[23]	Altered microbiome and serum metabolome profiles in fibromyalgia	Suggests diagnostic potential of multi-omics analyses
Minerbi et al[27]	Changes in serum bile acids and microbiome in fibromyalgia	Indicates a role for bile acid metabolism in fibromyalgia
Kim et al[28]	Less diverse microbiome and decreased propionate levels in fibromyalgia	Supports intestinal dysbiosis presence in fibromyalgia
Cummings et al[29]; Sudo et al[30]; Sudo[31]; Luczynski et al[32]; O' Mahony et al[33]	Impact of gut microbiome on pain perception and stress response	Implicates the microbiome in sensory and stress-related symptoms of fibromyalgia
Agostini et al[34]; Dai et al[35]	Probiotics reduce hypersensitivity and inflammation	Suggests probiotics as a treatment for fibromyalgia symptoms
Savignac et al[36]; Jia et al[37]; Markowiak-Kopeć and Śliżewska[38]	Probiotics improve depression, anxiety, and cognitive functions	Highlights potential of probiotics in managing fibromyalgia-related mood and cognitive issues
Aslan ÇİN et al[39]; Hinchado et al[40]; Cardona et al[41]; Roman et al[42]; Calandre et al[43]	Varied effects of probiotics/synbiotics on fibromyalgia symptoms	Indicates the need for further research on probiotics/synbiotics as fibromyalgia treatment
Surawicz et al[44]; Moayyedi et al[45]; Engen et al[46]; Xue et al[47]; Vrieze et al[48]	Efficacy of FMT in various conditions	Suggests exploring FMT for fibromyalgia treatment
Borody et al[49]; Pinn et al[50]; Xu et al[51]	Positive outcomes of FMT in CFS and IBS	Supports investigating FMT for fibromyalgia
Thurm et al[52]	Case report of successful FMT in fibromyalgia	Indicates potential of FMT in fibromyalgia treatment
Riordan et al[53]; Goebel et al[54]; Pimentel et al[56]	Link between SIBO, intestinal permeability, and fibromyalgia	Suggests SIBO treatment as a potential fibromyalgia therapy
Gezici[19]	Reduction in tender points after *H pylori* eradication	Supports exploring *H pylori* treatment in fibromyalgia
Hiippala et al[57]; Camilleri et al[58]; Li et al[59]; Baldi et al[61]	Dysbiosis affects SCFA production and inflammation	Points to SCFAs as a therapeutic target in fibromyalgia

CFS, chronic fatigue syndrome; FMT, fecal microbiota transplantation; GC-MS, gas chromatography–mass spectrometry; IBS, irritable bowel syndrome; ME, myalgic encephalomyelitis; SCFA, short-chain fatty acid; SIBO, small intestinal bacterial overgrowth.

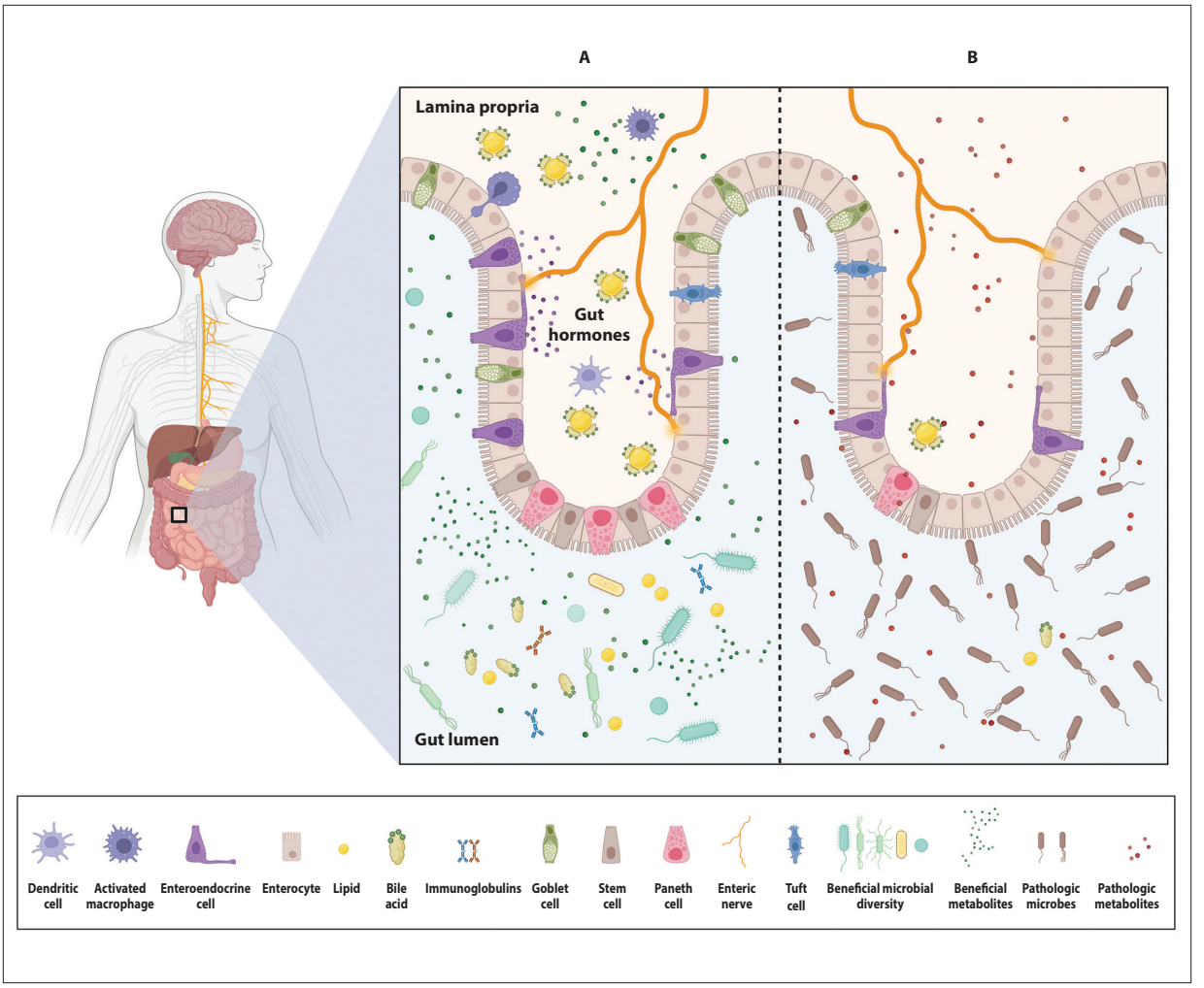

Figure 1. Healthy gut ecosystem (**A**) and proposed pathophysiology of fibromyalgia (**B**). Panel A illustrates the diversity of microbial species and beneficial metabolites in a healthy gut. Panel B depicts the effects of intestinal dysbiosis, including reduced microbiota diversity, bacterial overgrowth, and decreased beneficial metabolites, linked to systemic effects via the enteric nervous system and harmful metabolite absorption. Created with BioRender.com.

decades, the disease has been more clearly defined, and the prevalence of the disease has been reported to affect 2% to 6% of the US population.[4-6]

The diagnosis of fibromyalgia has progressed since its initial recognition by the American College of Rheumatology (ACR) in 1990 and subsequent classification by the World Health Organization in 1992. The ACR 2010 criteria introduced the Widespread Pain Index and the Symptom Severity Scale, focusing on pain areas and symptoms, such as fatigue and cognitive issues, that persist for at least 3 months.[6] Later revisions in 2011 and 2016 simplified these criteria for broader use, including self-reporting, and addressed previous limitations, such as the exclusion of tender point count.[7] The 2016 update merged elements from the 2010 and 2011 criteria, emphasizing generalized pain across multiple regions and the coexistence of symptoms with other diagnoses, reflecting a shift toward a more comprehensive and inclusive approach to diagnosing fibromyalgia.[7]

Despite the progress in our understanding of the disease's pathogenesis, the core mechanisms mediating the disease have yet to be defined. The multifactorial nature of fibromyalgia etiology, involving genetic and environmental contributions, underscores the complexity of its pathogenesis and the challenge of pinpointing a singular cause.[8] The condition's onset is often linked to stressors—physical, such as trauma or infection, or psychological. However, fibromyalgia symptoms can accumulate insidiously, with no discernible inciting event.

At the core of fibromyalgia pathology is central

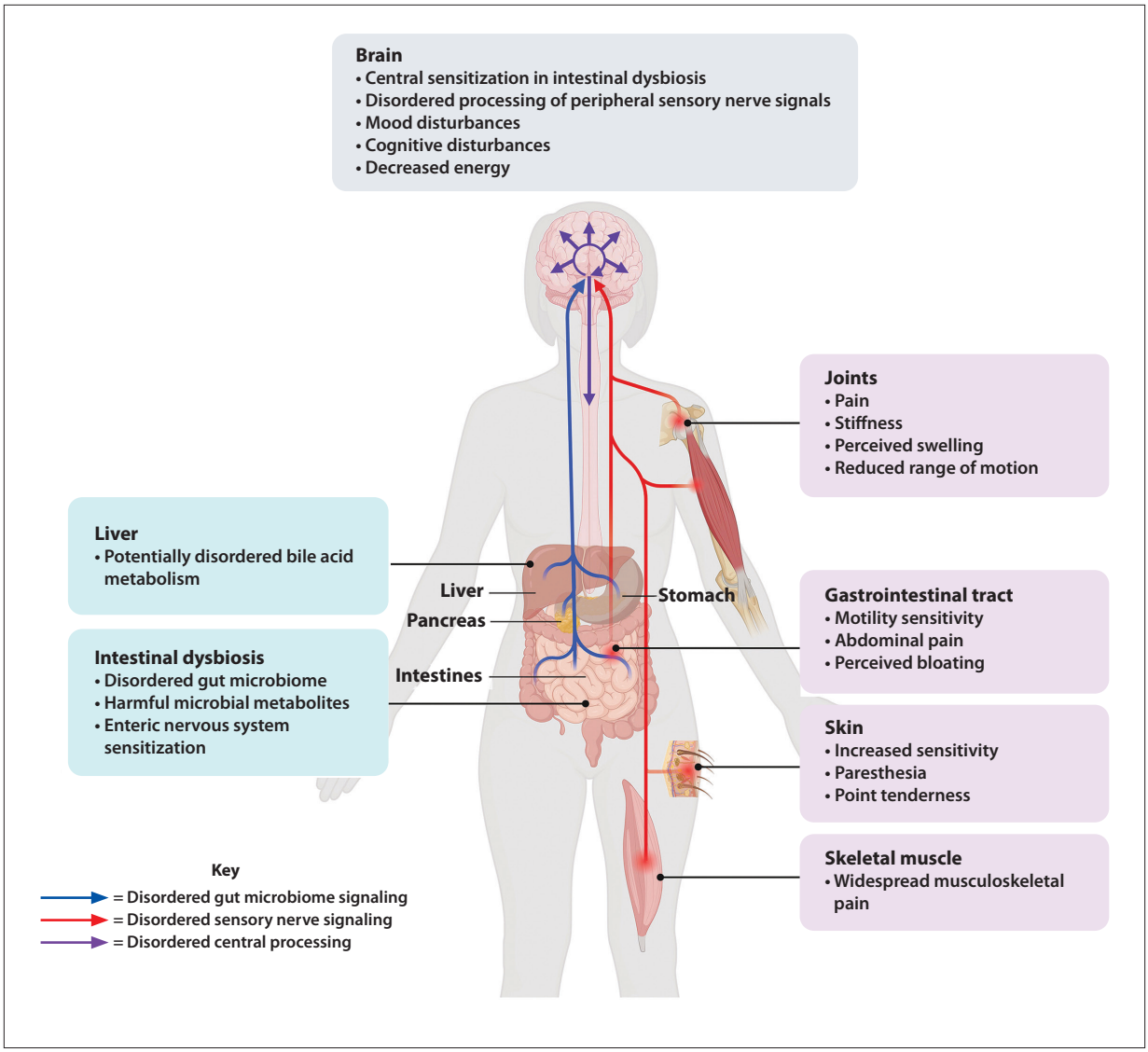

Figure 2. Conceptual framework linking intestinal dysbiosis to central nervous system alterations in fibromyalgia, suggesting a potential pathway by which microbial imbalances contribute to pain and cognitive symptoms through the gut-brain axis. Created with BioRender.com.

sensitization, wherein the central nervous system becomes primed to perceive pain more acutely.[9] This phenomenon of heightened pain sensitivity is a defining feature of fibromyalgia and has been shown to be modulated by various factors. The gut microbiome has recently emerged as a potential key mediator of central nociception through various mechanisms, representing a direct link between gut microbial composition and central sensitization, the defining characteristic of fibromyalgia.[8,10]

Dysbiosis, an imbalance in the gut microbiota, is often observed in fibromyalgia patients and may contribute to the disease's symptomatology through changes in gut permeability, immune activation, and systemic inflammation, amplifying central sensitization, thereby exacerbating pain symptoms. In this light, the gut-brain axis emerges as a potential pivotal mediator, facilitating a complex communication network that not only influences pain perception but also extends to mood and cognitive functions, which are frequently impaired in fibromyalgia.[10,11] The Table provides a comprehensive overview of research on the gut microbiome and fibromyalgia.

Furthermore, research in myalgic encephalomyelitis (ME) and chronic fatigue syndrome (CFS), conditions that overlap and share features with fibromyalgia, reinforces the notion that microbial exposure can precipitate an autoimmune response, indicating that similar reactions

might be implicated in fibromyalgia development. This autoimmune response, characterized by chronic inflammation, mirrors the systemic manifestations observed in ME, CFS, and fibromyalgia, suggesting shared pathophysiologic pathways that could be rooted in the gut microbiome's interaction with the host's immune system (Figure 1).[10,12]

This article summarizes the current literature in order to broaden clinical understanding of the role of the gut microbiome and its relationship to fibromyalgia, guide future research, and identify therapeutic targets.

Mechanism

The human gut microbiome, a complex ecosystem of bacteria, archaea, fungi, viruses, and protozoa, is integral to the physiologic, metabolic, and immune functions of the host. The bidirectional communication between the gut microbiota and the host suggests that the microbiome can affect a wide range of neurologic functions, including those related to pain conditions such as fibromyalgia.[10]

In fibromyalgia patients, the gut bacterial community composition is markedly altered, with specific bacterial species either increased or decreased in abundance compared with healthy controls. These shifts in bacterial abundance are not merely coincidental, as they have established metabolic activities that could be relevant to the development of fibromyalgia. Bacterial species may influence pain, fatigue, mood, and other fibromyalgia symptoms through the translocation of bacterial metabolites, such as short-chain fatty acids (SCFAs), bile acids, neurotransmitters, and bacterial antigens into the host's circulation. This interplay between the gut and the nervous system is the basis upon which the gut-brain axis is formed, and it further describes the bidirectional interplay between the regulatory systems (autonomic nervous system, immune system, and gut microbiome) and the effects on diverse disease processes (Figure 2).[10]

Although the intricacies of the pathways by which the microbiome modulates pain responses in fibromyalgia have yet to be defined, our current understanding suggests that gut bacteria could modulate nociception through the secretion of biologically active metabolites and pathogen-associated molecular patterns that interact with the host's immune system. In addition, metabolites such as SCFAs have been linked to pain sensation and immune regulation. Interestingly, although some SCFAs like butyrate can induce visceral hypersensitivity in animal models, they may have analgesic effects in humans, highlighting the complex and sometimes contradictory roles these substances can play.[10]

Emerging evidence has highlighted the role of the gut microbiota as a novel regulator of pain, which potentially implicates conditions like fibromyalgia. Modification in microbiota associated with chronic pain conditions has been observed, where dysbiosis in the gut microbiota regulates many aspects of host physiology, potentially leading to the development of overlapping chronic pain conditions, such as irritable bowel syndrome (IBS), chronic pelvic pain, and CFS. This suggests a broader role for the microbiome in the pathogenesis of chronic pain syndromes. Gut dysbiosis may induce or exacerbate existing symptoms, raising the question of whether interventions like antibiotics, fecal microbiota transplantation (FMT), and probiotics can modulate the gut microbiome to improve symptoms.[13]

Biomarkers

Considering the increasing evidence supporting the pathogenetic role of microbiome dysbiosis in fibromyalgia, various studies have investigated whether the gut microbial composition and its related metabolites could act as biomarkers of the disease.[14] The surrogates studied have ranged in nature from stool cultures[15] to *Helicobacter pylori* and small intestinal bacterial overgrowth (SIBO) testing, as well as microbiome and metabolomic studies.[16] Of particular importance is the study and identification of surrogates, which can help refine understanding of fibromyalgia pathogenesis and could provide potential diagnostic tools that would help clinicians objectively assess and monitor affected patients.

Given that an increased incidence of *H pylori* has been reported in patients with fibromyalgia, multiple studies have reported *H pylori* markers as potential surrogates. However, the data have been conflicting, with seropositivity for *H pylori* being reported to range from 30.8% to 68% in fibromyalgia groups compared with 17% to 44% in healthy control groups, with 2 studies reporting a statistically significant difference when comparing those groups.[17,18] In addition, a study examining *H pylori* presence in gastric biopsies or cultures of fibromyalgia patients reported an incidence of 78%, far above the expected incidence in the general population.[19] Yet, when *H pylori* positivity was assessed in fibromyalgia (42% positive) compared with an IBS cohort (46%), no statistically significant difference was observed (defined as positivity for any serologic assay, culture, or identification of *H pylori* on gastroduodenal biopsies). Overall, the evidence suggests that *H pylori* incidence is increased in fibromyalgia patients, having potential pathogenetic implications, but its value as a biomarker appears to be limited.

The advent of -omics technologies has changed the landscape of microbiome analysis. Current technologies that are frequently employed include 16S ribosomal

RNA gene sequencing, metagenomics, metatranscriptomics, metaproteomics, and metabolomics to evaluate microbiome phylogenic markers, genes, transcripts, proteins, and metabolites.[20] Recent studies have utilized these tools to evaluate microbiome profiles of patients with fibromyalgia compared with controls. In the first such study by Malatji and colleagues in 2017, urine metabolites were assessed in 18 fibromyalgia patients and compared with family/age-matched and young healthy groups and demonstrated that fibromyalgia patients exhibit significant increases in metabolites related to gut microbiome such as hippuric, succinic, and lactic acids.[21] Furthermore, the authors provided a predictive tool based on the levels of succinic acid, taurine, and creatine with robust diagnostic accuracy having a receiver operating characteristic (ROC) analysis of 90%. The samples from this cohort of patients were further investigated through gas chromatography–mass spectrometry, and 196 metabolites were identified. Their analysis suggested that metabolic dysregulation and intestinal dysbiosis are central to the pathogenesis of fibromyalgia.[22]

The alterations in the microbiome composition were subsequently studied by Clos-Garcia and colleagues in 2019 where they investigated the alterations of microbiome, serum metabolome, and cytokine profiling of 105 fibromyalgia patients and 54 matched controls.[23] This study demonstrated that the diversity of bacteria is reduced in the fibromyalgia setting with a significant decrease in *Bifidobacterium* and *Eubacterium* genera, which participate in host metabolism of neurotransmitters. This was further supported by the serum metabolome analyses that demonstrated altered levels of glutamate and serine. Lastly, the authors of this study performed multi-omics analyses to generate models that would have the potential to discriminate between fibromyalgia patients and controls. Their microbiome-based model was deemed to be the most accurate, having a ROC with an area under the curve (AUC) of 81%, indicating its potential as a diagnostic tool. This would warrant further investigation as to its specificity to fibromyalgia, as loss of microbiome diversity has been demonstrated in multiple conditions, including IBS,[24] inflammatory bowel disease (IBD),[25] and eczema.[26]

The observation that the intestinal microbiome is altered and could be used as a surrogate biomarker has been further supported by Minerbi and colleagues in 2019 where the whole genome sequencing-based analyses of the microbiome not only demonstrated significant alterations in its composition compared with controls but also correlated with the intensity of fibromyalgia symptoms.[11] Using machine learning algorithms, the authors generated a microbiome-based predictive model with an AUC of 87.8%. A subsequent study by the same group demonstrated that fibromyalgia patients have severe alteration in the relative abundance of bacteria known to metabolize bile acids.[27] This was accompanied by significant alterations in the levels of serum secondary bile acids with, importantly, a marked depletion in serum alpha-muricholic acid, the levels of which were highly correlated with the severity of pain intensity and fatigue. The authors generated statistical learning-based models that could accurately detect individuals based on the levels of serum bile acids. Those observations are notable as they were the first to directly implicate bile acid metabolism and serum level alteration in the pathogenesis of fibromyalgia with associated demonstration of intestinal microbiome changes. The study's findings set a strong foundation for further research into the bile acid–specific mechanisms implicated in fibromyalgia pathogenesis with potential associated diagnostic and therapeutic implications.

A study by Kim and colleagues in 2023 investigated the microbiome composition and stool SCFA levels and demonstrated that fibromyalgia patients have a less diverse microbiome than healthy controls and decreased propionate levels, further supporting the presence of intestinal dysbiosis in fibromyalgia.[28]

Treatment

The treatment of fibromyalgia has increasingly focused on microbiome modulation, given its role in the condition's pathogenesis. This section examines the effectiveness of various treatments like probiotics, prebiotics, synbiotics, and other innovative therapies. Each subsection delves into specific strategies, underscoring the importance of gut health in alleviating fibromyalgia symptoms and enhancing overall patient well-being.

Prebiotics and Probiotics

Given the multitude of microbiome-related mechanisms at play in the pathogenesis of fibromyalgia, a wide array of potential treatment strategies have been considered. The changes in biodiversity and composition of the host microbiome in patients with fibromyalgia led to microbiome-modulating strategies through the use of probiotics, prebiotics, and synbiotics as potential therapeutic options. Probiotics are defined as live microorganisms that confer a health benefit to the host when administered in adequate amounts. Prebiotics are fermentable dietary carbohydrates that can selectively stimulate growth and activity of beneficial gut microbiota members, particularly Bifidobacteria.[29] Synbiotics refer to products in which probiotics and prebiotics are combined.

Based on preclinical studies in germ-free (GF) mice, alterations in the gut microbiome have been shown to

affect visceral pain. Such studies have shown that GF mice exhibit visceral hypersensitivity accompanied by an increase in various cytokines (interleukin [IL]-6, IL-10, and tumor necrosis factor–alpha) and Toll-like receptor expression in the spinal cord. These changes were normalized by postnatal colonization with conventional microbiota, thus highlighting the importance of the gut microbiome in the homeostasis of colonic sensory neurons.[30-33] In turn, various studies have looked at the efficacy of probiotic administration on visceral hypersensitivity. A variety of strains have been assessed with benefits seen in dampening nociceptive response and reducing inflammation-induced hypersensitivity.[34,35]

In addition to visceral pain, research into the role of probiotics in mood and emotional modulation has gained attention. Probiotics have been shown to improve depression and anxiety via modulation of the hypothalamic-pituitary-adrenal axis and the gut-brain axis.[36] Probiotics and prebiotics can also bring about improvement in quality of life (QoL) and sleep disorders by the production of secondary bile acids, SCFAs, and neurotransmitters.[37,38] The use of probiotics, prebiotics, and synbiotics has been widely reviewed for IBS and CFS; however, data are limited regarding their use in fibromyalgia. Upon review of the available literature, 6 studies were found that assessed the efficacy of probiotics, prebiotics, or synbiotics in the treatment of fibromyalgia, including 5 randomized controlled trials (RCTs).

A double-blind, placebo-controlled randomized trial by Aslan ÇİN and colleagues in 2023 looked at probiotic or prebiotic supplementation vs placebo in 53 women with fibromyalgia.[39] Improvement in depression, anxiety, perceived pain, and sleep scores was seen in the probiotic group. The prebiotic group saw improvement in pain and sleep.

Another study looking at multiple factors in 15 patients with fibromyalgia with or without CFS before and after synbiotic administration showed improvement in multiple areas.[40] The authors found statistically significant improvement in levels of perceived depression, stress, anxiety, fatigue, and impact on daily activity in the total group of fibromyalgia patients. Although depression and stress only improved in fibromyalgia patients without a codiagnosis of CFS, anxiety, fatigue, and the impact of fibromyalgia only statistically improved in those with codiagnosis of CFS. After the intervention, fibromyalgia patients significantly decreased their systemic IL-8 concentration and increased their anti-inflammatory IL-10, but only in the group without codiagnosis of CFS. Additionally, the synbiotic generated an activation of the hypothalamic-pituitary-adrenal axis (physiologic cortisol release) as evidenced by elevated cortisol levels after the intervention that can compensate for the increased inflammatory status (elevated IL-8) observed at baseline in fibromyalgia patients.

Two probiotic intervention studies also looked at the effects of probiotics on cognitive functions, namely memory, attention, and impulsivity. One pilot RCT evaluated cognitive outcomes in 31 patients with fibromyalgia after administering a multistrain probiotic vs control for 8 weeks.[41] Results showed no effect on memory after treatment; however, there was an improvement in attention by reducing errors on an attention task. Specifically, a tendency to reduce errors of omission (Go trials) during the Go/No-Go Task was observed after treatment, although the effect was marginal and did not meet statistical significance. Another study looked at the effects on impulsivity, in addition to other factors, including QoL improvement and urinary cortisol, in 40 fibromyalgia patients receiving either probiotic vs control.[42] Their cognitive testing included the 2-choice task and Iowa gambling task. On the 2-choice task, there were improved numbers of impulse choices in the probiotic group. On the Iowa gambling task, there was a difference noted in separate repeated measures (learned test) and thus decreased impulsivity over time in the probiotic group.

While many of the studies showed improvement in various metrics with probiotic administration, one study showed no improvement in their primary or secondary outcomes.[43] This study looked at the administration of VSL#3 (a multistrain probiotic) vs control in 110 patients with fibromyalgia. The primary outcome was an improvement in the composite severity score of 3 main symptoms (abdominal pain, bloating, and meteorism), and the secondary outcomes included improvement in other gastrointestinal symptoms, fibromyalgia severity, depression, sleep disturbance, health-related QoL, and patients' overall impression of improvement. No differences were found between VSL#3 (n=54) and placebo (n=56) in the primary outcome (estimated treatment difference, 1.1; 95% CI, −2.1 to 4.2; *P*=.501), or in any of the secondary outcomes. Responders to VSL#3 were, however, more likely to maintain any improvement during the follow-up period compared with responders in the placebo arm.

The difference in results between these studies highlights the limitations of recent probiotic intervention trials. Study populations are small, outcome measures are varied, and the probiotics used are of variable strains, which precludes pooling and meta-analysis. Consequently, larger studies are called for to assess the efficacy of various probiotics and to determine potential standardized treatment regimens for patients. However, data support that probiotics in general may be of benefit in subjective measures of well-being, cognitive function, and decreased systemic inflammation, which in conjunction with their

safety profile, underline their therapeutic potential in fibromyalgia patients.

Fecal Microbiota Transplantation

FMT is delivered by oral capsules or the infusion of liquid filtrate feces from a healthy donor into the gut of an affected recipient and has been under investigation for use in an array of health conditions. The therapy is currently recommended for recurrent *Clostridioides difficile* infection.[44] FMT has also shown promising results for the treatment of IBD as well as for nongastroenterology conditions such as multiple sclerosis, Parkinson disease, obesity, insulin resistance, and metabolic syndrome.[45-48]

Given the emerging evidence of microbiome dysbiosis in chronic pain syndromes, including fibromyalgia, FMT has been investigated for use in functional disorders like IBS and CFS, suggesting a potential role in fibromyalgia treatment as well. In a study of 60 CFS patients treated with FMT, the clinical response rate was 70%, with 7 patients reporting full recovery 15 years out from treatment.[49] FMT was evaluated for use in the treatment of IBS in a single-center retrospective study by Pinn and colleagues in 2014.[50] Patients diagnosed with IBS who were not responsive to traditional treatment and had undergone FMT between 2011 and 2012 were identified and reviewed with questionnaires to assess their responses. In this study, 70% of patients experienced resolution or improvement of symptoms after FMT, specifically those with abdominal pain (72%), dyspepsia (67%), bloating (50%), and flatus (45%). Improvement of overall well-being was achieved in nearly half of the patients (46%). Given the similarities in microbiome disturbances in fibromyalgia, these findings may support exploring FMT as a potential therapeutic avenue for fibromyalgia, although direct research in this area is still needed to confirm its efficacy and safety.

A meta-analysis was performed by Xu and colleagues in 2019 looking at use of FMT in patients with IBS, with only 4 RCTs meeting their criteria for inclusion.[51] In this analysis, which included a total of 254 participants, there was no significant difference in global improvement of IBS symptoms observed at 12 weeks in FMT vs placebo (relative risk [RR]=0.93; 95% CI, 0.48-1.79). Heterogeneity among studies was significant (I^2=79%). However, subgroup analyses revealed benefits of single-dose FMT using colonoscopy and nasojejunal tubes in comparison with autologous FMT for placebo treatment (number needed to treat = 5, RR=1.59; 95% CI, 1.06-2.39; I^2=0%). The Grading of Recommendations Assessment, Development and Evaluation quality of the body of evidence was very low. The heterogeneous nature of the various studies and overall small study populations make it challenging to draw conclusions regarding the efficacy of FMT in IBS; however, multiple other clinical trials are currently ongoing.

Regarding the use of FMT in fibromyalgia, data are very scarce and limited to a successful case report published in 2017 describing the use of FMT in a 58-year-old male with fibromyalgia, IBS, and CFS refractory to standard treatments resulting in significant disability. The patient was interested in FMT but given that it was not approved for his conditions he used an online protocol for FMT and self-instilled the fecal transplant using an enema 6 times. These treatments resulted in a gradual improvement of symptoms, with reported full recovery 9 months after the last treatment. Next-generation sequencing analysis was performed before the first FMT and after the last FMT, with the most prominent alterations at the genus level, including a decrease in fecal *Streptococcus* proportion from 26.39% to 0.15% and an increase in *Bifidobacterium* from 0% to 5.23%.[52] To our knowledge, this is the only report in the literature describing the use of FMT in fibromyalgia, and there are currently no active clinical trials for use in these patients. There is, thus, a lot that remains to be explored in this regard, as results have been promising for several conditions.

Antibiotic Therapy and Treatment of Small Intestinal Bacterial Overgrowth

SIBO has been known to cause increased intestinal permeability in various disorders.[53] Patients with fibromyalgia have been found to have increased intestinal permeability, as determined by measurements of urinary disaccharide excretion (which reflects intestinal uptake) in a study by Goebel and colleagues in 2008.[54] Increased intestinal permeability can lead to luminal products passing through the epithelial layer, gaining abnormal access to both the intestinal and extraintestinal immune system.[55] Changes in the intestinal barrier can, in turn, lead to increases in inflammation as well as autoimmunity and systemic disease.

The link between fibromyalgia and SIBO has been documented in part of a study comparing rates of abnormal breath testing in fibromyalgia patients, IBS patients, and controls. In the fibromyalgia cohort, 42/42 (100%) patients had abnormal breath tests compared with 3/15 (20%) controls. Additionally, the degree of somatic pain in the fibromyalgia group correlated significantly with the hydrogen level seen on the breath test (r=0.42, P<.01).[16] In another study, the impact of SIBO treatment on symptom improvement has been investigated in 111 IBS patients who underwent a lactulose breath test (LBT) and were then randomized into 2 treatment groups (neomycin or placebo). Following treatment, the patients returned for repeat LBT, and symptom questionnaires were administered. At baseline, 84% of the

study population had abnormal LBT results. Neomycin administration resulted in a 35% composite score on the symptom questionnaire compared with 11.4% for the placebo. Patients also reported 35.3% bowel normalization after neomycin compared with 13.9% for placebo. A graded response to treatment was seen, such that the best outcome was observed if neomycin was effective in normalizing the LBT (75% improvement; one-way analysis of variance, P=.0001).[56] Given the abnormalities in LBT in fibromyalgia patients and the associated worsening of symptoms, treatment of SIBO in these patients may be of benefit; however, future studies are needed to investigate its effectiveness specifically in the fibromyalgia population.

In addition to therapeutic targets of the microbiome on a more global level (ie, probiotics and FMT), targeting specific pathogens has also been investigated as a potential therapeutic strategy. *H pylori* in particular has been implicated as a possible player in the pathogenesis of fibromyalgia. A 2011 study by Akkaya and colleagues measured serum *H pylori* immunoglobulin G (IgG) and IgG by enzyme-linked immunosorbent assay technique in patients with fibromyalgia and controls.[17] Seropositivity of *H pylori* IgG antibody in the fibromyalgia patients was significantly higher than in the control group (P=.25). Another study performed in Egypt also found a higher prevalence of *H pylori* IgG antibody in 68 patients with primary fibromyalgia syndrome compared with 32 controls (P<.001).[18] In this study, higher levels of post-exertional pain (P=.0307), morning stiffness (P=.0177), confusion (P=.0139), depression (P=.0015), mood disturbance (P=.0093), anxiety (P=.0388), tension headache (P=.0088), sleep disturbance (P=.0046), and changes in appetite (P=.0301) were seen in fibromyalgia patients with *H pylori* seropositivity compared with those without. Patients who were *H pylori* positive, when compared with patients who were *H pylori* negative, also had higher visual analog scale scores of fatigue (P<.001), global severity (P=.0017), and anxiety (P<.001); a higher fibromyalgia impact questionnaire score (P<.001); more tender points count (P<.001); and a longer duration of illness (P<.001).

Based on the premise that *H pylori* may have an implication in the pathogenesis of fibromyalgia and in the symptomatology of the disease, it has been hypothesized that eradication may help patients with the condition. One such study included 32 fibromyalgia patients with dyspeptic complaints.[19] Patients with *H pylori* confirmed by culture were assessed by the number of tender points, the Pittsburgh Sleep Quality Index, the Beck Depression Inventory, and the Beck Anxiety Inventory pre- and post-treatment for eradication of *H pylori*. In the study, triple therapy with amoxicillin 1 g, clarithromycin 500 mg, and lansoprazole 30 mg was given twice daily for 3 weeks to all patients. The number of tender points was significantly reduced post-treatment compared with baseline (P<.001). However, there were no significant differences between pre- and post-treatment scores for the Beck Depression Inventory, the Beck Anxiety Inventory, and the Pittsburgh Sleep Quality Index (all P>.05).

Dietary Interventions, Nutraceuticals, and Emerging and Experimental Therapies

As described, alteration in SCFAs is another significant pathogenic consequence of dysbiosis-related breakdown of the intestinal barrier. Such dysbiosis permits leakage of lipopolysaccharides and decreased secretion of SCFAs by commensal microbiota, in turn leading to increased inflammatory cytokine production,[57,58] enhanced pain sensitization[59] and neuro-inflammation.[60] Alterations of SCFA levels in fibromyalgia patients have recently been reported, finding significantly altered composition of SCFA-metabolizing bacteria as well as alterations in serum and urine levels of SCFAs.[11,22]

To the best of our knowledge, no studies have looked at SCFA supplementation directly as a therapeutic target for fibromyalgia. However, one randomized, double-blind crossover trial looked at the replacement of Khorasan grain (products made with *Triticum turgidum* ssp turanicum) in the diet of patients with fibromyalgia and the resulting changes in SCFA levels, intestinal microbiota composition, and symptom scales.[61] In comparison with the control wheat diet, the Khorasan wheat diet had more positive effects on intestinal microbiota composition, fecal immune profiles, and SCFA profiles. Specifically, there was a nearly statistically significant increase in butyric acid levels (P=.054). The authors also reported a positive correlation between the increased level of the phyla Actinobacteria, Verrucomicrobia, Candidatus Saccharibacteria, and Bacteroidales on various symptom outcome scales (related to sleep, pain, function, and fatigue), metabolic composition, and downstream effects on symptoms in persons with fibromyalgia.

Bile Acid Metabolism Modulation

Despite recent studies reporting significantly altered bile acid metabolism observed in fibromyalgia patients,[27] there are currently no reports in the literature describing therapeutic interventions targeted at modulating the bile acid cycle. Given the multilevel alterations described in the form of bile acid–metabolizing bacteria and serum bile acid level changes, it would be of particular interest to investigate compounds such as ursodiol and cholestyramine, which have been extensively studied in the past and have overall benign safety profiles, in future therapeutic trials of fibromyalgia.

Conclusion

The pathogenesis, diagnosis, and management of fibromyalgia are complex; however, progress has been made in identifying gut microbiome changes related to the condition. The current literature highlights the intricate and important role that the gut microbiome plays in the pathogenesis and symptomatology of fibromyalgia. As diagnosis of fibromyalgia can be challenging, identification of microbiome-related biomarkers as additional diagnostic tools would be helpful for clinicians. There are multiple pathways in which the gut microbiome of fibromyalgia patients can be targeted as therapy for the condition; these pathways provide a road map for future studies. Future investigative efforts should target larger human studies, as sample sizes of most studies thus far have been small, and should include fibromyalgia patients, as more robust data exist for patients with other functional disorders such as IBS and CFS. The role of the gut microbiome in fibromyalgia remains an exciting and clinically significant topic for further exploration.

Disclosures

The authors have no relevant conflicts of interest to disclose.

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