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# Gut–Pain Connection Reaffirmed by Microbiome Differences in Fibromyalgia Patients and Controls

People with fibromyalgia have different microbiomes from controls, according to a recent study.

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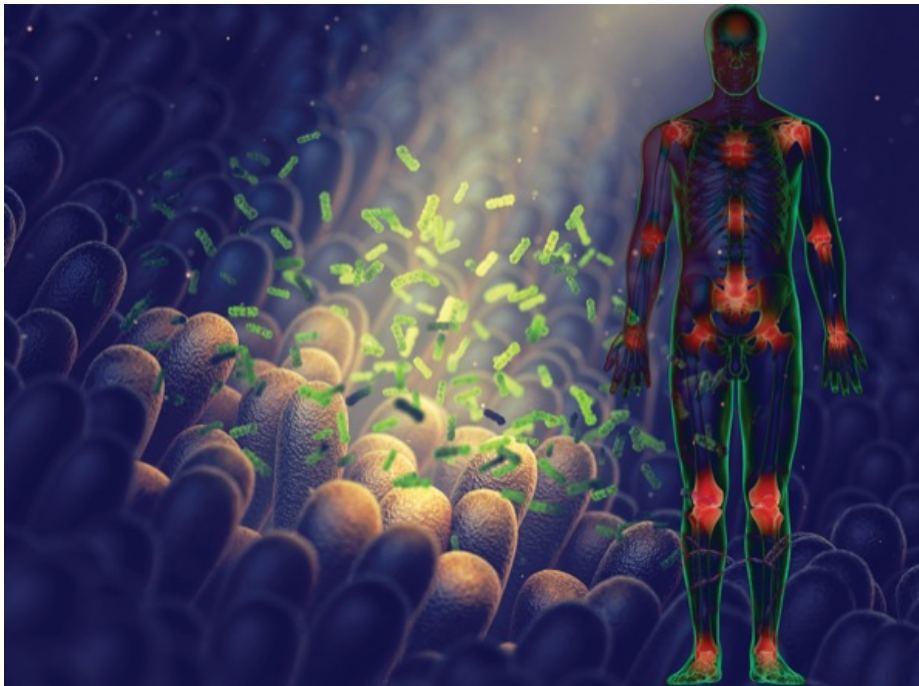
“The abundance of some of these bacterial species correlates with the severity of fibromyalgia symptoms—pain, fatigue, cognitive symptoms and impaired sleep,” said first author Amir Minerbi, MD, PhD. Artificial intelligence algorithms could automatically distinguish patients from controls, based on only the composition of their gut microbiome.

“The demonstration of objective findings separating fibromyalgia patients from healthy controls provides convincing evidence that fibromyalgia is a real syndrome,” said Dr. Minerbi, a clinical research fellow at the Alan Edwards Pain Management Unit at McGill University Health Center, in Montreal.

“This is the first demonstration of gut microbiome alteration in nonvisceral pain,” the investigators wrote.

The study included 77 women with fibromyalgia and 79 healthy controls. A pain physician verified the diagnosis of each participant, and each was thoroughly characterized, including dietary habits, demographic characteristics, comorbidities and

medications, Dr. Minerbi said (*Pain* 2019 Jul 2. [Epub ahead of print]. doi: 10.1097/j.pain.0000000000001640).



Stool samples from each were analyzed for bacterial DNA, and blood samples were analyzed for bacteria-derived metabolites.

The investigators used advanced computational algorithms to examine the differences in microbiomes between patients and controls, as well as the possibilities for interactions among potentially confounding variables, including medications, diet and physical activity, among others, Dr. Minerbi said.

Co-author Emmanuel Gonzalez, PhD, a bioinformatics specialist at the Montreal Node of the Canadian Centre for Computational Genomics, used AI algorithms to distinguish patients from controls based only on the composition of their microbiomes. They did so accurately 87% of the time.

“Variance in the composition of the microbiomes was explained by fibromyalgia-related variables more than by any other innate or environmental variable,” according to the report. Additionally, that variance was “correlated with clinical indices of fibromyalgia in line with observed alteration in butyrate-metabolizing species, targeted serum metabolite analysis, verified differences in the serum levels of butyrate and propionate in fibromyalgia patients,”

the investigators wrote.

Rajat Bhatt, MD, a rheumatologist in independent practice at Prime Rheumatology, in Richmond and Pearland, Texas, said the research fails to explain certain phenomena such as that patients with fibromyalgia who travel abroad will have a change in the gut microbiome that does not mitigate or otherwise change the patient's symptoms. Additionally, he said when patients with fibromyalgia undergo a colectomy, for reasons unrelated to fibromyalgia, the fibromyalgia is neither resolved nor altered.

Dr. Minerbi responded, "Out of the 1,620 different bacteria found in the guts of study participants, only 72 were significantly altered in individuals with fibromyalgia—approximately 4.5% of all bacterial taxa. Of these, some were increased and others decreased. It is thus unlikely that nonspecific interventions such as colectomy or travel abroad would have a specific effect on the abundance of these bacteria."

"FM [fibromyalgia] is a heterogeneous condition, meaning there are inherent differences in who develops it and how/why they do," said Andrea L. Nicol, MD, an assistant professor of anesthesiology at the University of Kansas School of Medicine in Lawrence.

"However, it is not exactly clear whether ... individual differences are accounted for in the results," Dr. Nicol said. "Despite these limitations, their approach and data are highly original and lend credence to the need for further investigations in this area."

The authors stated that the hypothesis that alterations of the microbiome may affect pain processing and perception has been supported by several animal studies showing "that gut microbiota play an important role in the development of visceral pain of chemotherapy-induced neuropathic pain, and of opioid tolerance."

Human studies have shown "consistent alterations in individuals with irritable bowel syndrome (IBS) and in patients suffering from

chronic dysfunctional pelvic pain,” according to the report.

“Similarly, patients with chronic fatigue syndrome (CFS), which shares some symptomatic features with fibromyalgia, were shown to have altered gut microbiome and metabolomics profiles.” Additionally, alterations of microbiome have also been reported in several rheumatologic diseases, the investigators wrote.

“Some patients have noticed that nutrition has a significant effect on their symptoms; introducing or eliminating certain nutrients may improve or aggravate their symptoms,” Dr. Minerbi said. “These reports, by many patients, plus the growing body of literature regarding the importance of the gut microbiome in so many other conditions, led us to take this unexplored avenue.

“To test this hypothesis, we chose fibromyalgia, as it is a prevalent, poorly understood syndrome, which is difficult to diagnose and to treat and which leads to significant suffering and disability in affected patients,” Dr. Minerbi said.

Dr. Nicol said, “Certainly, if these findings can lead to potential diagnostic parameters that would help clinicians have an objective measure for the condition, this would undoubtedly change the current knowledge frame for fibromyalgia diagnosis, which is currently based on a self-report questionnaire.”

*—David C. Holzman*