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EDITORIAL

Small Is Big: Why the Analysis of the Fecal Microbiome Provides Little Important Information on IBS Severity

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IBS is one of the most common gastrointestinal (GI) disorders, significantly affecting the quality-of-life of affected individuals and increasing health care costs. Several hypotheses regarding the etiology of IBS posit that the human gut microbiome contributes to IBS pathogenesis [1]. In fact, diarrhea-predominant IBS (IBS-D) was the first luminal GI disorder to receive FDA approval for a microbiome-modulating drug, rifaximin, a poorly absorbed antibiotic, that improves abdominal pain, stool consistency/frequency, urgency and bloating in IBS-D and mixed IBS patients, which implies that the gut microbiome contributes to the pathogenesis of IBS [3]. Nevertheless, no studies to date have identified a consistent fecal microbial metagenomic pattern that correlates with IBS or its severity at a single timepoint.

In this issue of *Digestive Diseases and Sciences*, Wang et al. [4] performed an elaborate study of the correlations between the stool microbiome and IBS by assessing the metagenomic composition of fecal microbiota and short chain fatty acids (SCFAs) among IBS subjects with IBD severity separated into discrete groups (n = 55) compared with controls (n = 28). A longitudinal observational study was performed with two timepoints 4 weeks apart, at which fecal material was collected and microbiota and SCFAs were profiled. Furthermore, questionnaires were administered enabling the calculation of the IBS Symptom Severity Score, as well as quality of life (QoL), stool pattern, dietary intake, and anxiety and depression scores.

Over time, the severity group of 36% of IBS subjects changed. Stool microbial alpha and beta diversity were similar between IBS severity groups and controls. Changes in the stool microbiome between the two time points were not different between the groups, suggesting that the temporal stability of the stool microbiome was the same in the IBS severity groups and controls. In addition, changes in the stool microbiome of IBS subjects did not correlate with changes in severity. Analysis at the genus level revealed that only *Bifidobacterium, Terrisporobacter* and *Turicibacter* relative abundance was consistently different at both timepoints between the IBS and control groups. These differences did not predict symptom severity. When data from both timepoints were included, individual variation and IBS explained ($R^2 = 70\%$) and ($R^2 = 2\%$) of the total stool microbiome variation, respectively. Anxiety and depression scores did not explain the dynamism of the stool microbiome. SCFA composition also did not predict IBS severity and was not correlated with psychological factors over time. In conclusion, a consistent stool microbiome and SCFA "signature" associated with IBS severity were not found.

The study by Wang and colleagues has multiple important translational and clinical implications: Currently, there are several commercially available stool tests which provide patients with detailed analysis of the stool microbiome composition. As shown by Wang et al., while > 70% of the stool microbiome variability is explained by the individual participants' microbiome variation, < 3% of the variation is explained by IBS disease itself. This emphasizes that it is unlikely that simply describing the composition of the fecal microbiome will provide useful information regarding the etiology or treatment of IBS. Considering the current state of knowledge of stool microbiome in IBS, deep sequencing analysis of individual stool microbiomes offers little or no actionable results in clinical practice to guide therapy or prognosis.

Another interesting finding of the study by Wang et al. is the lack of association between longitudinal dynamism in the stool microbiome and anxiety and depression scores. This finding underscores that psychological factors are more likely epiphenomena of IBS rather than causal factors

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capable of directly changing the microbiome, as suggested by central sensitization models of IBS [5].

Despite the pathophysiologic contribution of the microbiome to IBS based on the aforementioned studiers of rifaximin, a universal stool microbiome signature for IBS and IBS severity has not been described. Aligned with this concept, swinging the stool microbiome composition toward that of healthy donors via fecal microbiome transplantation does not consistently improve symptoms [6]. Furthermore, rifaximin, a microbiome modulation drug which has improves all of the cardinal symptoms of IBS-D, has only minimal and transient effects on the stool microbiome composition [7], in contrast to the effects of rifaximin on the small bowel microbiome in the same phase III trial [3] (TARGET 3), in which IBS-D subjects who had abnormal lactulose breath tests consistent with small intestinal bacterial overgrowth (SIBO) were 4.3 times more likely to respond to rifaximin compared with those with negative baseline breath tests (59.7% vs. 25.7%; P = 0.002; odds ratio 4.3, 95% CI, 1.5–12.7) [8]. Moreover, the response rate to rifaximin was even higher in subjects whose breath tests normalized after treatment (76.5%). These findings emphasize the potentially more important contribution of the small bowel microbiome to the pathogenesis and treatment of IBS. To address this concern, the REIMAGINE (Revealing the Entire Intestinal Microbiota and its Associations with the Genetic, Immunologic, and Neuroendocrine Ecosystem) study has aimed to investigate the importance of the microbial populations of the small bowel and their contribution to human health and disease [9]. Results from this study have shown that the small bowel microbiome is markedly different from the fecal microbiome and also varies between bowel segments. The influence of compositional changes of the small bowel microbiota to human disease states, however, remains incompletely understood.

Though stool collection is advantageous as it is easily obtainable without invasive procedures, small bowel microbiome analysis maybe able to provide more precise and granular data regarding the diagnosis and treatment of IBS, in particular the functioning of the"microbiome-gut-brain axis" that posits that the gut microbiome produces bioactive molecules that release serotonin from enterochromaffin cells, alter serotonin metabolism, and affect the gut and brain "connectome," all of plausibly altering gut motility, secretion, and sensation as part of IBS pathogenesis [10–12].

The study of the microbiome and its correlation with disease processes has been a point of interest in the medical community. The study by Wang et al. has improved knowledge of the topic. Expanding understanding of the function of the gut microbiome will likely provide key data regarding the pathogenesis in addition to identifying novel biomarkers useful in diagnosis, disease classification, and therapeutics in IBS and other gastrointestinal disease states.

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