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EDITORIAL

Microbial dysbiosis in spouses of ulcerative colitis patients: Any clues to disease pathogenesis?

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Abstract

A number of alterations have been found within the gut microbial profile of patients with inflammatory bowel diseases when compared with the healthy population; however, it is unclear whether such dysbiosis is the cause or simply the consequence of the disease state. In ulcerative colitis, the environment seems to play a crucial role in disease etiology since monozygotic twins show a concordance rate of only 8%-10% - though it is unclear whether it does so by acting through the microbiome. In this study, the authors investigated the influence of cohabitation on the gut microbial community in healthy partners of ulcerative colitis patients - with the intent of clarifying some of these issues. As expected, ulcerative colitis patients had a significant dysbiosis and alterations in microbial metabolism. Interestingly, these abnormal fecal microbial communities were relatively similar amongst patients and their spouses. Thus, this study shows that the microbial profile might be partially transferred from ulcerative colitis patients to healthy individuals. Whether this finding impacts on disease development or has any implication for the role of the microbiome in inflammatory bowel disease etiology remains to be determined.

Key words: Ulcerative colitis; Cohabitation; Spouses; Gut microbiome

Core tip: Dysbiosis in inflammatory bowel diseases is common. However, microbial dysbiosis could be a consequence, rather than cause of the disease state. In this study the authors detected dysbiosis and altered microbial metabolism not only in ulcerative colitis patients but also in their healthy cohabiting partners. Therefore, the microbiome might be partially transferred from ulcerative colitis patients to healthy individuals. Since spouses of ulcerative colitis patients do not have an increased risk of developing the disease this study suggests that dysbiosis might be an effect rather than the cause of the disease. Overall, the precise role of the microbiome in inflammatory bowel

disease etiology remains unknown.

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Man has coexisted with microbes since the beginning of time. We bear trillions of microbes in our body. Indeed, this symbiotic microbial cell population (or microbiome) has been reported to outnumber that of the human host by 10:1 - though more recent estimates appear to validate such ratio only when considering human nucleate cells[1]. The largest portion of the microbiome is located in the gastrointestinal tract and functions as a digestive organ, a training tool for the immune system, and a guardian of harmful infections[2]. A number of factors can affect the microbial community in the gut--both in healthy and diseased states-- and include diet, age, medical therapy, smoking, and genetics[3]. Many human diseases have been linked to an altered gut microbiota. Among those, the most studied are the inflammatory bowel diseases (IBD) - both Ulcerative colitis (UC) and Crohn's disease (CD). Several alterations (dysbiosis) have been found in the gut microbial profile of IBD patients including a decrease in diversity, *Bacteroides, Firmicutes, Clostridia, Ruminococcaceae, Bifidobacterium, Lactobacillus, and F prausnitzii*; an increase in *Gammaproteobacteria*; and the presence of adherent invasive *E. coli* and *Fusobacterium*[2]. Altered microbial function has also been reported in IBD patients-specifically, butyrate, butanoate and propanoate metabolism are decreased while the oxidative stress, the type II secretion system, secretion of toxins, the transport of both amino acids and sulfates are increased[2].

Despite these impressive and reproducible alterations in the gut microbiome of IBD patients, it is unclear whether such dysbiosis is the cause or simply the consequence (*i.e.*, bacterial adaptation for survival) of the disease state. This is a major mechanistic issue with a potential crucial impact on development of new medications and on IBD management. Current evidence supports both views. For example, disease activity seems to affect the microbial profile in IBD while microbial alterations similar to those described in IBD have been described in patients with nonspecific intestinal injury[4]. These observations suggest that the microbial profile in IBD might be the result of local changes in the intestinal mucosa following the disease onset. On the other hand, dysbiosis also seems to be associated with genetic polymorphisms. In addition, immune mediated colitis can be elicited in genetically susceptible mice with single commensal bacterial species[4]. Thus, these findings highlight the potential role of the microbiome in IBD etiology.

As for the individual IBD's, studies in monozygotic twins show a concordance rate of 44%-55% in CD and only 8%-10% in UC[5]. Thus, the environment seems to play a crucial role in disease etiology - especially in UC - though it is unclear whether it does so by acting through the microbiome.

In the paper published in the 25th issue of the Journal, Chen *et al*[6] studied the influence of cohabitation on the gut microbial community in healthy partners of UC patients using 16S rRNA amplicon sequencing. Fecal samples were collected from 8 UC patients and their healthy partners at Lishui People's Hospital in China. Fecal microbial communities showed a higher similarity among UC patients than in their healthy partners (*i.e.*, the partners' group was more heterogeneous). As a whole, UC patients had a lower relative abundance of bacteria belonging to the *Firmicutes* - especially *Blautia*, *Clostridium*, *Coprococcus* and *Roseburia*. In addition, the microbiome of UC patients showed a greater lipid and nucleotide metabolism. Microbiota dysbiosis and altered microbial metabolism were detected in both UC patients and their healthy partners, with the most relevant genera in the latter group being *Akkermansia*, *Bacteroides*, *Escherichia*, *Lactobacillales*, *Klebsiella,* and *Parabacteroides*. Importantly, using 3 different types of analysis the authors showed that the entire microbiota of UC patients was not significantly divergent from those of their partners. Healthy partners of UC patients also showed an increased microbial membrane transport and metabolism of cofactors and vitamins.

The authors concluded that microbial composition and metabolism in healthy partners of UC patients may be impacted by cohabitation.

This is a small study without follow up which would have possibly clarified if the altered microbiome in spouses of UC patients may eventually impact on their health and bear any clinical meaning. No information is given regarding the number of samples per study subject and whether samples were collected the same day(s) by patients and their spouses. Furthermore, there were differences in age and sex distribution between the UC group and the spouses' group. This difference might bear implications for microbial profile heterogeneity[3]. Also, based on C-reactive protein levels, the disease activity was not uniformly distributed among UC patients - another potential source of heterogeneity in the microbial profile results. The methodology used by the authors in this study - 16S rRNA gene sequencing - is sound and more accurate than culture dependent methods used in many similar studies[7]. The authors' conclusions are reasonable and apparently support an important role of the environment in changing the gut microbiome - in this case, the UC microbiome modifying the bacterial profile of their healthy cohabiting partners. The study does not clarify whether the transfer of the microbiome might occur by direct contact or by other means.

To lend more weight to the authors' conclusion

in this and similar types of studies, IBD and any unrelated upper GI condition should be duly excluded in cohabiting spouses. While disease is unlikely in the absence of symptoms, the hypothetical concomitant presence of IBD in the spouses could clearly explain the similarities between their microbial profile and that of their patient partners. Furthermore, in the Chen *et al*[6] study only the stool bacteria were tested; however, the stool microbiome might be different from the intestinal tissue microbiome - which more closely represents the intestinal mucosa flora[2]. Finally, the microbial profile of individuals cohabiting with IBD patients should also be compared with that of healthy controls living in the same geographical area and socio-economic conditions to minimize the impact of unrelated environmental factors. The microbial profile of the Asian population might differ from that of the Western population[8] - an important factor to keep in mind in comparative studies.

So, does this study suggest that the microbiome dysbiosis in IBD might be a primary event rather than the result of the disease? The answer is no. This study shows that the environment might influence the microbial profile in healthy individuals; however, the impact of such change on disease development remains unclear. Likely, dysbiosis in and by itself is insufficient to cause disease. Indeed, there is no evidence that cohabitation with IBD patients might increase the risk of disease in the spouses, so the results of this study only indicate that the microbiome can be partially transmitted from individual to individual. The final microbial profile in each individual - whether healthy or not - might be the result of the very complex nature of the microbial development process[9], which evolves over time and is affected by a number of factors[3].

CONCLUSION

The findings of this study support the well-known observation that cohabitation is indeed a way to share our microbial cell population with family members, or even with our dogs[10]. Whether this impacts disease development or points to a specific role of the microbiome on IBD etiology remains to be determined.

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