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Invited Editorial

Gut Feelings Matter: The Unresolved Questions of Irritable Bowel Syndrome-Like Symptoms in Inflammatory Bowel Disease in Remission

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Lay Summary

Even when remission is achieved in inflammatory bowel disease (IBD), gastrointestinal symptoms may persist. These can be classified as irritable bowel syndrome (IBS)-like symptoms in IBD in remission. Further scientific research and debate are required to clearly define this entity and to improve the quality of IBD care.

Keywords: IBS-like symptoms, IBD remission, persistent symptoms

In an effort to determine therapeutic goals in inflammatory bowel disease (IBD), the "selecting therapeutic targets in IBD (STRIDE) initiative" has been launched and an updated second version has been published in 2021.[1] While objective indicators of adequate treatment of inflammation in IBD such as biomarkers, and endoscopic and histological parameters are deemed relevant treatment targets, the strongest recommendations emphasized clinical response and clinical remission as immediate and medium-term goals, respectively. The presence of gastrointestinal symptoms has a significant negative impact on overall well-being in patients with IBD.[2] Therefore, the focus on "gut feelings" is justified, and aiming at symptom relief is imperative when evaluating the effects of treatments. The STRIDE-II defines clinical response and remission based on the reduction of symptoms such as abdominal pain and stool frequency in Crohn's disease (CD) and stool frequency and rectal bleeding in ulcerative colitis (UC).[1] However, a major challenge in clinical practice and research is that many patients who achieve inflammatory remission still experience gastrointestinal symptoms. These persistent symptoms can affect the outcomes of clinical trials, potentially underestimating the anti-inflammatory efficacy of treatments. In clinical practice, these cases often present diagnostic and therapeutic dilemmas, leading to unnecessary diagnostic procedures or treatment modifications that fail to provide adequate symptom relief, ultimately causing patient dissatisfaction. There is a need for robust definitions of causes of persistent gastrointestinal symptoms in IBD in remission and clear guidance on diagnostic and therapeutic approaches. However, there are several challenges. First of all, the possible etiology of these symptoms is diverse and can be multifactorial. Residual or ongoing inflammation may be present and could drive symptoms. But also resolved inflammation may result in complications such as fibrosis, strictures, fistulas, and damage to the intestinal epithelium. As a consequence, gut dysmotility, post-inflammatory visceral hypersensitivity, or absorptive dysfunction may cause persistent symptoms. Also, undiagnosed co-existent conditions such as celiac disease may generate symptoms in patients with IBD. And lastly, the effects of altered gut-brain interaction may manifest as irritable bowel syndrome (IBS)-like symptoms in IBD in remission.[3] The latter is probably a frequent phenomenon in IBD, but this entity is not well defined in medical literature, and the prevalence, underlying mechanisms, diagnostic approaches, and optimal treatments are largely unexplored. A meta-analysis showed that the pooled prevalence of IBS-like symptoms in IBD in remission is as high as 32.5%, indicating that one in 3 patients with IBD who reach inflammatory remission still experience significant gastrointestinal symptoms. However, the same study brought to light the limitations of poor definitions. First of all, defining remission based exclusively on symptoms is obviously inadequate, as IBS-like symptoms may persist even in the absence of inflammation. Relying on biomarkers such as fecal calprotectin and C-reactive protein is suboptimal as well due to their limitation in diagnostic accuracy. Although endoscopic, histological, and radiological evaluations may be the gold standard, they are often unavailable in large cohort studies.[4] In this issue of *IBD*, Bjorn Christian Olsen et al. present a study aiming to reliably define the prevalence of IBS-like symptoms in IBD in remission.[5] Their cohort study followed newly diagnosed IBD patients (both CD and UC), with a 1- and 3-year follow-up moment. The researchers

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defined inflammatory remission based on biochemical markers in 283 IBD patients (fecal calprotectin < 250 µg/g) and in a large subgroup of 224 patients, based on endoscopic evaluation. The presence of IBS-like symptoms was defined by the Rome IV criteria for IBS. Their key finding was the prevalence of IBS-like symptoms in IBD in remission of 21.9% when remission was based on fecal calprotectin levels. This prevalence was 19.2% when remission was defined based on endoscopic evaluation. Furthermore, the researchers showed that during the 3-year follow-up, the prevalence of IBS-like symptoms slightly decreased. Inflammatory bowel disease patients who suffered from IBS-like symptoms experienced more fatigue and reported reduced health related quality of life compared to those who did not meet the Rome IV criteria for IBS. And consistent with studies in IBS patients in the general population, there was a female predominance in IBS-like symptoms in IBD in remission. Using these definitions for both inflammatory remission and IBS-like symptoms in IBD, this Norwegian study demonstrated that IBS-like symptoms in IBD in remission are indeed prevalent, affecting about one in 5 patients with IBD.[5] But this percentage is lower when compared to the pooled data published previously.[4] Nevertheless, further studies from diverse geographic regions using the same methodology are needed to determine global prevalence. Moreover, scientific consensus is necessary to clearly define the entity of IBS-like symptoms in IBD in remission. The Rome IV criteria for IBS were neither developed nor validated for use in patients with IBD.[6] Moreover, in clinical practice, a diagnosis of IBD precludes the diagnosis of IBS. To add to the challenges, as IBD is a dynamic condition, characterized by alternating episodes of flares and remission, a possible diagnosis of IBS-like symptom in IBD in remission cannot be static. And alternative explanations for persistent gastrointestinal symptoms should always be considered in patients with IBD.[3]

Improving our comprehension of the gut-brain interaction in IBD is imperative. Not only to better understand the origins of IBS-like symptoms in IBD in remission, but pathways along the gut-brain axis may also hold clues to improve anti-inflammatory treatment in IBD. The neuroimmunological mechanisms may open new pathways for treatment and possibly even be the key to break the current therapeutic ceiling.[7] Effects of the central nervous system on the intestines, mediated by psychological stress, have been shown to negatively affect the maturation of the enteric nervous system in young age in rodents.[8] Such a process could contribute to mechanisms by which people with childhood trauma have higher chances of developing IBS later in life.[9] Furthermore, psychological stress has been shown to directly activate the intestinal immune system and drive inflammation in IBD via the hypothalamic-pituitary-adrenal axis and via enteric glial cells.[8] These pathways may place the enteric nervous system and gut-brain interaction at the center of IBD pathophysiology. However, further research is imperative.

In conclusion, to be able to optimally meet our treat-to-target strategies in IBD as defined by the STRIDE-II and to achieve clinical response and remission for the maximum number of patients, it is essential to take into account IBS-like symptoms in IBD in remission. Efforts are needed to develop clear, standardized definitions for both inflammatory remission in IBD and IBS-like symptoms in IBD in remission. By refining our approach to these "gut feelings" in IBD, we can ensure that remission truly translates into a better quality of life for patients.

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Conflicts of Interest

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