A Key Role for the Small Bowel in Irritable Bowel Syndrome Pathophysiology: Time to Refocus?

References

1. Wong DK, et al. Clin Gastroenterol Hepatol 2020;18:449–456.
2. Branco F, et al. Arq Gastroenterol 2007;44:58–63.
3. Squadrito G, et al. Cancer 2006;106:1326–1330.
4. Momosaki S, et al. J Viral Hepat 2005;12:325–329.
5. Squadrito G, et al. J Hepatol 2013;59:696–700.
6. Seto WK, et al. Immunosuppressives: advancements, applications and analyses. Nova Science Publishers, Hauppauge, NY. 2017:41.
7. Raimondo G, et al. J Hepatol 2019;71:397–408.
8. Mulrooney-Cousins PM, et al. PLoS Pathog 2014;10:e1004332.
9. Wong DK, et al. Liver Int 2017;37:995–1001.
10. Testoni B, et al. J Hepatol 2019;70:615–625.
11. Debes JD, et al. Ann Hepatol 2019;18:786–787.
12. Debes JD, et al. Lancet Gastroenterol Hepatol 2019;4:581.
13. Feng Z, et al. Am J Gastroenterol 2019;114:530–532.

Conflicts of interest
The authors disclose no conflicts.

Most current article

https://doi.org/10.1016/j.cgh.2020.03.058

A Key Role for the Small Bowel in Irritable Bowel Syndrome Pathophysiology: Time to Refocus?

Dear Editor:

We read the article by McOmber et al[1] with great interest. In this study, the authors show that small intestinal permeability, measured by the ratio of orally ingested and urinary excreted lactulose/mannitol, is increased in first-degree relatives of children with irritable bowel syndrome (IBS) and functional abdominal pain, whereas no differences were found for colonic or gastroduodenal permeability. This study provides additional evidence for the key role of intestinal barrier dysfunction in IBS. The hypothesis for this study was based on previous findings that indicate that the barrier function of the small bowel is impaired in IBS patients, mostly in patients with the diarrhea-predominant subtype (IBS-D).[2,3] Data on colonic permeability and barrier function in patients with other IBS subtypes remain inconclusive.[2,3]

Historically, IBS has generally been considered a disorder of the large bowel, hence the previous terminology, eg, spastic colon, nervous colon, or irritable colon syndrome. However, accumulating evidence suggests the involvement of the entire gastrointestinal tract, including an important role for the small intestine. On cellular and molecular level, several alterations in small intestinal tissue samples of patients with IBS, in particular in IBS-D, have been shown. These include transcriptional and post-transcriptional mechanisms, controlling tight-junction protein dysfunction with disrupted apical junctional complex integrity.[4,5] Furthermore, an increased number of mast cells is found in small bowel epithelium of IBS patients compared with healthy controls, which may modulate intestinal barrier dysfunction and visceral sensitivity.[5] Increased gut permeability has also been associated with visceral hypersensitivity, which is a defining characteristic of IBS.[6] Small intestinal distention is associated with pain, indicating that increased mechanosensation in the small bowel may play a role.[7] In addition, recently we have shown that peppermint oil capsules that release in the small intestine have greater beneficial effects on symptom relief in IBS patients compared with the colonic release formulation,[8] supporting the notion that the small bowel is an important target for treatment.

In conclusion, although the small bowel function is difficult to study, the current[1] and previous findings[2–5,7,8] point to a key role for this organ in the pathophysiology of IBS, which may be a feasible focus for new therapies. Uncovering the exact relationship between gut barrier dysfunction and symptom generation will be an important step in understanding the development of IBS, yet still more research is needed in this respect.

ZLATAN MUJAGIC, MD, PhD
Division of Gastroenterology-Hepatology
NUTRIM School of Nutrition and
Translational Research in Metabolism
Maastricht University Medical Center
Maastricht, The Netherlands

DAISY M. A. E. JONKERS, PhD
Division of Gastroenterology-Hepatology
NUTRIM School of Nutrition and
Translational Research in Metabolism
Maastricht University Medical Center
Maastricht, The Netherlands

AD A. M. MASCLEE, MD, PhD
Division of Gastroenterology-Hepatology
NUTRIM School of Nutrition and
Translational Research in Metabolism
Maastricht University Medical Center
Maastricht, The Netherlands

DANIEL KESZTHELYI, MD, PhD
Division of Gastroenterology-Hepatology
NUTRIM School of Nutrition and
Translational Research in Metabolism
Maastricht University Medical Center
Maastricht, The Netherlands

References

1. McOmber M, et al. Clin Gastroenterol Hepatol 2020;18:375–384 e1.
2. Mujagic Z, et al. Aliment Pharmacol Ther 2014;40:288–297.
3. Dunlop SP, et al. Am J Gastroenterol 2006;101:1288–1294.
4. Martinez C, et al. Gut 2013;62:1160–1168.
5. Robles A, et al. Neurogastroenterol Motil 2019;31:e13718.
6. Zhou Q, et al. Pain 2009;146:41–46.
7. Accarino AM, et al. Gastroenterology 1995;108:636–643.
8. Weerts Z, et al. Gastroenterology 2020;158:123–136.

Conflicts of interest
These authors disclose the following: Daisy Jonkers has received funding from public-private partnership grants from the Carbohydrate Competence Center and Top Knowledge Institute (TKI) / Well on Wheat. For the execution of the

study by Weerts et al (reference 8), Ad A. M. Masclee and Daniel Keszthelyi have received a ZonMw (The Netherlands Organization for Health Research and Development [Dutch government]) health care efficiency grant and an unrestricted research grant from Will Pharma SA. The remaining author discloses no conflicts.

Most current article

https://doi.org/10.1016/j.cgh.2020.03.026

Proactive Measures Aimed at Improving Appropriateness of Use of Proton Pump Inhibitors in Clinical Practice

Dear Editor:

We read with great interest the article by Lin et al[1] that was recently published in in *Clinical Gastroenterology and Hepatology*. The authors report on the impact of an educational program aimed at improving the appropriateness of proton pump inhibitors (PPIs) in a large health system in the United States.[1] Indeed, we feel that the issue covered by Lin et al, despite being the topic of a long-standing clinical problem with a clear social and health impact, is still timely and relevant. For example, despite several published studies highlighting the inappropriateness of PPI prescriptions in ambulatory care,[2–4] and the efforts by scientific societies both in the United States and Europe to educate physicians in the appropriate use of long-term PPIs,[5,6] PPIs are still widely and inadequately prescribed in clinical practice.[3,7,8] In Italy, in 2018, PPIs ranked second among the most prescribed classes of drugs, accounting for 7% of the yearly pharmaceutical expenditure, while in the United States approximately 10% of ambulatory patients are PPI users.[7,8]

The proactive measures implemented within the Harris Health System are essential to reach the target of PPI de-prescription. The intervention acted at 2 levels: the primary care providers and the patients. It relied on an educational program, an electronic prescription system, and patient handouts. With this intervention in place, they managed to significantly decrease unique PPI prescriptions by 16.5%.[1] However, one of the most relevant findings of their study is that informed discussion with the primary care provider was the main driving factor that led to a positive outcome. This finding is of particular relevance, as other recent studies have highlighted the fact that patients may take unwise decisions regarding long-term PPIs' discontinuation, with potential catastrophic downfalls, and that only 24% of patients had previously discussed the risks and benefits of therapy with their providers.[9]

In order to improve long-term PPI treatment in ambulatory care, we recently implemented a program aimed at identifying inappropriate long-term PPI prescriptions among patients referred to our outpatient clinic, independent from the reason for referral, and to recommend a step-down protocol similar to the one followed by Lin et al,[1] with eventual discontinuation of PPI treatment and the use antacids to avoid acid secretion rebound.[2,9-11] Among 143 patients referred to our outpatients clinic who were on long-term (ie, >8 weeks) PPI therapy for gastroesophageal reflux disease, we found that 35.0% of them were taking the drug inappropriately. Following specialist counseling, a protocol of PPI tapering and withdrawal was put in place in 81.7% of them.

We feel that processes aimed at increasing the appropriateness of PPI prescription through education-guided decisions and empowerment of patient-prescriber interactions should be implemented at all levels to improve adequacy of treatment, decrease the potential of side effects, and reduce costs associated to inadequate therapies. We agree with Lin et al[1] that every effort should be actively pursued to improve the quality of our patient care.

EDOARDO G. GIANNINI, MD, PhD
GIORGIA BODINI, MD, PhD
MANUELE FURNARI, MD
ELISA MARABOTTO, MD, PhD
Gastroenterology Unit, Department of Internal Medicine, University of Genoa, IRCCS-Ospedale Policlinico San Martino, Genoa, Italy

References

1. Lin D, et al. Clin Gastroenterol Hepatol 2020;18:763–766.
2. Crespi M, et al. Dig Liver Dis 2019;51:173–174.
3. Lassalle M, et al. Eur J Clin Pharmacol 2020;76:449–457.
4. Heidelbaugh JJ, et al. Am J Manag Care 2010;16:228–234.
5. Freedberg DE, et al. Gastroenterology 2017;152:706–715.
6. Savarino V, et al. Dig Liver Dis 2018;50:894–902.
7. https://www.aifa.gov.it/documents/20142/0/Rapporto_OsMed_2018.pdf/c9eb79f9-b791-2759-4a9e-e56e1348a976 [accessed on March 26th, 2020].
8. Bustillos H, et al. PLoS One 2018;13:e0208461.
9. Kurlander JE, et al. Am J Gastroenterol 2019;114:244–249.
10. Giannini EG, et al. Dig Dis Sci 2006;51:1904–1909.
11. Targownik L. Am J Gastroenterol 2018;113:519–528.

Conflicts of Interest
The author discloses no conflicts.

Most current article

https://doi.org/10.1016/j.cgh.2020.04.027

Diets and Hepatocellular Carcinoma: The Emperor's New Clothes

Dear Editor:

The conclusion by Yang et al[1] that "replacing animal or dairy fats with vegetable fats, or replacing saturated fats with monounsaturated or polyunsaturated fats, was associated with reduced risk of hepatocellular carcinoma (HCC)" deserves robust comment.

First, the report was one more post hoc (retrospective) analysis among thousands from the Nurses' Health