Zinc Deficiency and Intestinal Permeability in the Context of Rational Diagnostic and Drug Development for Diarrhea-Predominant Irritable Bowel Syndrome

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Diarrhea-predominant irritable bowel syndrome (IBS-D) is a symptom-based condition defined by the presence of concurrent abdominal/sensory symptoms of pain and bowel/motor symptoms of diarrhea. For the many patients that meet these criteria, there are several etiologies to explain its pathogenesis recognizing the possibility of concurrent and overlapping explanations in light of the increasing complexity of the current understanding of human gut–brain–microbiome interactions [1]. Though there are now several targeted therapies that are applicable to patients with IBS-D, the need to develop companion diagnostics to identify subsets of patients who might particularly respond to any given treatment is becoming increasingly clear—even for investigational treatments that are at early stages of development.

In this issue of *Digestive Diseases and Sciences*, Rezazadegan, et al. [2] present a retrospective case–control study of patients that were diagnosed with IBS-D compared with age- and sex-matched healthy controls, reporting lower serum zinc levels among IBS-D patients compared with healthy controls. Particular strengths of this study include its use of the up-to-date Rome IV criteria to identify patients with IBS and the inclusion of measurements of dietary intake using reliable and valid instruments with the intent in part of evaluating the contribution of zinc supplementation toward reducing IBS symptom severity [3].

Their present work fits within a broader set of the literature addressing human intestinal paracellular permeability that was recently reviewed by Camilleri et al. [4] as an important paradigm and avenue for the rational development of future diagnostic and treatment targets. In particular, the

hypothesis that zinc supplementation might ameliorate the symptoms of IBS is certainly intriguing based on its known promotion of wound healing and increasing mucosal barrier integrity [5]. Of note in the present study, the authors also found higher serum zonulin levels among IBS-D patients. Their findings suggest that serum zinc levels appear to inversely correlate with IBS-D symptom severity and that higher levels of serum zonulin appear to inversely correlate with serum zinc levels. As the authors suggest, there are several points to consider when interpreting these findings that warrant further discussion while also suggesting substantial areas for further research and development that are indeed ongoing in the field.

Zonulin (pre-haptoglobin 2, or preHP2) has been proposed as a mediator of tight junction permeability that is directly applicable to the broad proposed concept of “leaky gut” as a contributor to the pathogenesis of IBS [6]. Unfortunately, and as the authors discuss, the use of zonulin remains controversial as a measure of intestinal permeability due to challenges in reliably measuring zonulin levels using standard commercial ELISA kits and also the lack of a publication to our knowledge that describes a direct correlation between serum zonulin and standard measures of intestinal paracellular permeability [4, 6–8]. Other methods used to evaluate intestinal permeability have been used in prospective studies, including the use of urine lactulose and mannitol excretion that reflect the luminal absorption (and subsequent excretion) of substrates that are typically poorly absorbed via transcellular solute pathways, recognizing that these studies account for the several complex variables of location of absorption (small bowel vs. colon and related sites of luminal fermentation), the small mass of these disaccharides, and the relatively recent development of HPLC mass spectrophotometric assays for reliable detection [4, 9].

As the authors suggest, the present retrospective study overall proposes three exploratory questions and avenues for further prospective research that are needed prior to

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advocating broad implementation of these findings in practice:

1. Is intestinal paracellular permeability a valid biomarker for IBS?
2. Does increased intestinal permeability provide important clues toward elucidating the pathogenesis of IBS?
3. Does the restoration of increased intestinal permeability improve the symptoms of IBS?

To resolve these questions in further studies, reliable tests remain sorely needed in order to translate findings from in vivo animal models to human studies that can support a pathophysiologic basis for the rational development of targeted therapy for patients affected by IBS, functional dyspepsia, and other related disorders, a critical need stated by Camilleri et al. and several others [4]. These tests should also be sufficiently responsive to any proposed interventions to both demonstrate increased intestinal paracellular permeability and its resolution. Once a pathophysiologic rationale is demonstrated, investigational treatments will also need to show that objective response correlates with patient-reported outcomes that are inherent to the diagnosis and experience of patients affected by disorders of gut–brain interaction [10].

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Disclosures EDS consulted for Bausch Health and GI Supply outside the scope of the current work.

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