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Commentary

Tissue is the Issue: Duodenal Biopsies to Elucidate Gut Structure and Function Among Undernourished Children in Low-Resource Settings

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As the largest surface area tissue interface of humans with their environment, the small intestinal epithelium is simultaneously tasked with absorbing essential nutrients from food, while protecting against a vast array of microbes, toxins, and waste products in the gut lumen (Canny and McCormick, 2008). When these functions are chronically compromised—e.g., by frequent gut infections, inflammation, undernutrition, or combinations thereof—the consequences in young children may include persistent changes to the mucosal architecture of the gut, intestinal barrier defects, dysbiosis, metabolic derangements, impaired immunity, growth failure, mortality, and neurodevelopmental disability (Moore et al., 2011; Victora et al., 2010). In low- and middle-income countries (LMICs), a vicious cycle of infection and undernutrition in early childhood often leads to chronic linear growth stunting, a condition affecting 1 in 3 children. Moreover, even the best nutritional interventions prevent only one-third of the typical chronic linear growth deficit seen among children in Asia and Sub-Saharan Africa (Black et al., 2013; Dewey and Adu-Afarwuah, 2008). This points to a critical unmet need for effective interventions to prevent and reverse chronic gut injury and dysfunction among children in low-income countries.

How will we get there? In high-income countries, upper gastrointestinal endoscopy is routinely performed in children with known or suspected enteropathies (Tringali et al., 2017), allowing for gold standard diagnostics and precious research specimens for scientific discovery. Ample access to gastrointestinal tissue biopsies has, in turn, facilitated a vastly improved understanding of pediatric onset enteropathies such as celiac disease, eosinophilic gastrointestinal disease, and inflammatory bowel disease. In low- and middle-income countries; however, persistent disparities in food security, access to healthcare, and research infrastructure have led to an unacceptable reality in which far less is known regarding the pathophysiology and clinical management of malnutrition-associated and environmental enteropathies (conditions first described in developing countries in the 1960′ and 70′ s) (Chacko et al., 1969) vs. rarer, 21st century pediatric GI conditions such as eosinophilic esophagitis. Well-justified attention to the significant ethical, logistical, and scientific quandaries (e.g., appropriate age-matched controls) inherent in obtaining gastrointestinal biopsies from children in low-resource settings must be balanced by an acknowledgement that progress towards breakthroughs has lagged from a paucity of studies.

Against this background, Amadi et al. recently report in *EBioMedicine* findings from their analyses of small intestinal biopsies in 34 Zambian children with severe acute malnutrition (SAM) and persistent diarrhea (PD, duration 14 days or greater) and 61 adult controls (Amadi et al., 2017). In these participants, and in an additional 101 child controls, they measured biomarkers of enterocyte damage, microbial translocation and systemic inflammation in blood and gut secretions. Applying careful measurements of crypt, villous, and epithelial surface area dimensions, they find that epithelial surface area was reduced in children with SAM and PD relative to healthy adults. Further, they identify perturbations of histology, claudin-4 and E-cadherin expression and localization in children with SAM and PD. Along with other markers of gut-to-blood bacterial translocation, serum LPS was higher in children with SAM and PD vs. healthy children. Intriguingly, serum antibodies associated with untreated celiac disease (anti-transglutaminase (TTG) and anti-deamidated gliadin peptide (DGP)), were elevated within the normal range in children with SAM and persistent diarrhea vs. healthy adults. Further, higher antibody levels correlated with reductions in villus height. This is intriguing because of the overlap in histological appearance between malnutrition enteropathy, environmental enteropathy, and celiac disease—previously known as “non-tropical sprue”.

How specific are elevations in TTG and DGP autoantibodies to celiac disease? Recently, Le Fevre et al. have published findings on elevated TTG antibodies in almost a quarter of children with eosinophilic esophagitis (Le Fevre et al., 2017). In addition, they review previous studies in which elevated serum TTG antibodies have been found in non-celiac disease states, including malnourished patients with cerebral palsy, alcohol consumers, and IBD and other autoimmune conditions. In the Le Fevre study, the presence of duodenal eosinophils was associated with elevated TTG antibodies, opening the door to look for similar correlations between duodenal eosinophilia and TTG antibodies in biopsies from children in the Zambian study (all of whom were negative for stool parasites at the time of endoscopy).

Despite the tremendous value of duodenal biopsies to diagnosis and discovery, they are not without limitations. Similar to controversies regarding the patchiness of celiac disease small intestinal pathology, individual biopsy specimens in malnutrition-associated enteropathies may ultimately exhibit considerable variation from site to site within the same patient. Such patchiness might, in turn, confound correlation of morphometry results with systemic biomarkers. Amadi and colleagues are to be commended for their noteworthy study, which applies meticulous and cutting-edge analysis to identify potential structural and molecular targets to reverse the functional barrier defects of malnutrition enteropathy in children. If confirmed in subsequent investigations, their study also highlights the potential use of serum autoantibodies as surrogate biomarkers of enteropathy. Depending on the temporal relationship of autoantibody elevation to small intestinal injury, autoantibodies might conceivably be used to screen children at risk of SAM and PD or, alternatively, non-invasively monitor gut responses to experimental interventions in clinical trials. The gut pathophysiology of SAM, PD, and subclinical environmental

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enteropathy awaits further exploration in a variety of clinical and epidemiologic settings. The study by Amadi and colleagues adds valuable information to move this field forward on behalf of children at the greatest risk.

Conflict of Interest

Together with Amadi and colleagues, Drs. Syed and Moore serve as members of the Environmental Enteric Dysfunction Biopsy Initiative Consortium, a program funded by the Bill & Melinda Gates Foundation.

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