Zonulin and Pediatric Celiac Disease

Permeability of the intestinal tract is thought to play a role in the development of celiac disease (CD), and markers for intestinal permeability would be helpful in discovering the pathogenesis of this disorder. Zonulin is involved with tight junction function between intestinal epithelial cells, and high zonulin levels are associated with increased intestinal permeability. Thus, the authors of this study evaluated intestinal permeability changes in children prior to a diagnosis of CD.

This study used data from the Celiac Disease Genomic Environmental Microbiome and Metabolomic study (CD-GEMM). CD-GEMM is a prospective study following children who have a first degree relative with CD, and such children are followed over time with serial blood and stool samples as well as clinical information obtained. The authors used data from CD-GEMM study subjects enrolled between 2014 and 2022 from both Italy and the United States. All patients had blood samples obtained every 6 months for the first 3 years of life and then annually. Parental diaries and other clinical information, including a subject's age at gluten introduction, number of respiratory and gastrointestinal viral infections, and antibiotic exposure were recorded. Celiac antibody and human leukocyte antigen genotype testing occurred in all subjects. Study subjects were diagnosed with celiac disease autoimmunity if they had elevated celiac antibody titers on at least two separate occasions. Study subjects were diagnosed with CD if they had histologic changes consistent with CD on endoscopic duodenal biopsy or had elevation of celiac antibody titers that met criteria for CD per recommendations from the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition. Patients with celiac disease autoimmunity and CD were combined into one group labeled as "celiac disease autoimmunity" (or CDA). This group of patients with CDA was compared to matched controls, and serial serum zonulin levels were obtained in both study and control patients.

A total of 51 study subjects with CDA were compared to the same number of controls. It was noted that 63.7% of subjects were female with 31.4% of enrolled subjects being from the United States (68.6% being from Italy). Gluten introduction occurred at 7.9 months for controls and 8.3 months for patients with CDA. Follow-up time averaged 15.5 months for all study subjects.

Mixed effect longitudinal modeling demonstrated a steeper slope differential that was statistically significant for increased zonulin levels in patients with CDA compared to controls. This steeper slope indicating higher zonulin was present 6 to 78 months before a diagnosis of CDA. Study subjects from Italy had a higher mean zonulin level compared to children from the United States. A subject's age at initial gluten introduction and amount of gluten ingested did not account for zonulin level changes. Although the number of viral infections did not increase the risk of CDA, the use of antibiotics significantly increased the risk of CDA occurring. Antibiotic use, especially multiple rounds of antibiotics, also increased zonulin levels more rapidly.

This study demonstrates that zonulin levels may be a useful marker for intestinal permeability in the setting of pediatric patients who are at risk of developing CD. Perhaps increasing zonulin levels also may prove to be a diagnostic technique to predict CD in pediatric patients. The association of antibiotic use and rising zonulin levels suggests that intestinal microbiome changes potentially can lead to CD which further enforces the importance of antibiotics stewardship.

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Infant Symptoms are Often Misdiagnosed as GERD

Infants in the newborn intensive care unit (NICU) are often diagnosed with gastroesophageal reflux disease (GERD); however, symptoms such as back arching and irritability are non-specific and may not be associated with GERD events. This issue is important as gastroesophageal reflux (GER) is a normal physiological process which often does

not correlate with GERD symptoms. The authors of this study used the technique of 24-hour pH / impedance monitoring to determine if symptoms of infant back arching and irritability were associated with acidic GERD.

This retrospective study from a U.S. tertiary children's hospital evaluated all pH / impedance probe studies done at their institution over an 8-year period. All included studies had a minimum of 18 hours of recorded data. Infants older than 52 weeks postmenstrual age, infants on proton pump inhibitor therapy at the time of the pH-impedance study, and infants with no outcome data at one year were excluded. All included infants in the study underwent chest radiography to confirm probe placement, and all studies occurred with patients in the supine position. An infant in the study was considered to have frequent arching and irritability if greater than 72 such events occurred during a typical pH / impedance probe study. Symptom-associated probability between infant symptoms and documented GER events was determined by the Fischer Exact Test, and any acid GER event or bolus event occurring 2 minutes before a symptom of arching and irritability was considered a related GERD event.

In total, 516 infants were evaluated by pH / impedance monitoring for which 297 of infants in the NICU had arching and irritability. The median gestational age for study infants was 30.1 weeks, and the median age at the time of pH / impedance monitoring was 41.7 weeks. No significant difference in arching and irritability was present between male and female infants when comparing infants with less than 72 arching and irritability events and infants with 72 or more arching and irritability events. A total of 4456 out of a total 39,973 arching and irritability events were associated with a bolus-associated GERD (11.1% of events). A total of 3062 out of 39,962 arching and irritability episodes were associated with acidic GERD (sensitivity = 8%) while a total of 246,462 out of 262,534 events were not associated with acidic GERD (specificity = 94%). The authors noted a positive predictive value for arching and irritability episodes of 17% for bolus GERD events and 16% for acidic GERD events. The negative predictive value for both bolus GERD and acidic GERD events was 87%. Acidic GER events were not significantly different between infants with less than 72 arching and irritability episodes and infants with 72 or more arching and irritability episodes. However, infants with GERD episodes during a bolus feed were more likely to have arching and irritability episodes.

Infants with 72 or more arching and irritability episodes were statistically more likely to have a history of prematurity, history of oral feeding, neurologic disease, or chronic lung disease. At one year post study, such infants were significantly more likely to have undergone fundoplication.

This study provides further evidence that symptoms related to GERD in infants are over diagnosed. In NICU infants with excessive arching and irritability episodes, no significant correlation was noted in relation to increased acidic reflux during pH / impedance monitoring. Instead, infants with excessive arching and irritability episodes appeared to have other significant health issues not related to GERD. This study demonstrates that infants with perceived irritability and arching likely have other causes to their symptoms instead of GERD which should be considered. Additionally, this study provides evidence that acid suppression therapy likely was not needed in most of these infants as there was minimal correlation of GER to symptoms.

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