

EDITORIAL

Amount May Beat Timing: Gluten Intake and Risk of Childhood Celiac Disease



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In the current issue of *Clinical Gastroenterology and Hepatology*, Aronsson et al¹ from The Environmental Determinants of Diabetes in the Young (TEDDY) study group explore the relationship between gluten intake and risk of celiac disease (CD) in genetically at-risk children. Although the data in this nested case-control study originated from Sweden where the rate of CD is highest, the TEDDY study group has its scientific center in Florida, and a novel by one of that state's most famous authors may serve as an introduction to this article. In Ernest Hemingway's book *The Sun Also Rises*, two of the main characters, Bill and Mike, discuss financial matters, and Bill asks: "How did you go bankrupt?", and Mike answers, "Two ways. Gradually, then suddenly."

This article shows that even if you introduce gluten gradually into an infant's diet, the child can still develop CD suddenly. Children with early diagnosed CD had a lower gluten consumption at 6 months of age than controls (albeit nonsignificant), but children with CD consumed larger amounts of gluten later at the age of 1–2 years than genetically predisposed children who did not subsequently develop the disease. Because of the abundant previous literature on infant feeding^{2–14} and other risk factors,^{15,16} what does this article add?

It actually adds a lot. In recent years, prospective cohort studies^{9,11,17} and 2 randomized clinical trials^{13,14} have shown that age at gluten introduction and breastfeeding duration may be less important for the risk of developing CD (at least in childhood) than previously thought. However, no earlier study has used prospectively collected data to investigate the range of gluten quantity in early infant nutrition and risk of CD.

Aronsson et al¹ analyzed a subset of the prospective cohort TEDDY study, matching 146 Swedish children with CD with 436 controls. The authors found that for each additional gram of gluten consumed per day before tissue transglutaminase seroconversion, the risk of future CD increased by 28%. They also found that

children receiving large amounts of gluten (>5 g per day) during their first 24 months had a 2.6-fold increased risk of CD compared with those who consumed lower quantities. Importantly, the relationship between the intake of gluten and underlying HLA in patients did not differ.

Although the study should be commended for its rigorous study design, particularly the efforts to measure the amount of gluten intake, some questions remain.

The appropriate approach of an infant feeding study would be to examine previously reported infant feeding risk factors, and that was clearly done in this study. Neither breastfeeding duration (odds ratio [OR], 0.99) nor age at first gluten introduction (OR, 0.99) was associated with future CD. However, the picture gets blurred when the authors suggest that their findings should be taken into account for future infant feeding recommendations, likely meaning the amount of gluten offered to children at risk of CD.

It is not yet clear what such infant feeding recommendations should be. Although the highest gluten consumers had a doubling of CD risk (OR, 2.65; 95% confidence interval [CI], 1.70–4.13) in this study, the total amount of gluten intake was only marginally increased in CD cases vs controls (OR, 1.05; 95% CI, 1.01–1.10), an association that decreased when individuals with first-degree relatives with CD were excluded. One might speculate that mothers with CD themselves may differ in how they breastfeed and introduce gluten to their children, but earlier data from Sweden suggest that is not the case¹⁸; thus, the lack of statistical significance when excluding first-degree relatives could be a chance finding. Autoimmune disease is more common in first-degree relatives of patients with CD.¹⁹

The authors do not report on the amount of gluten consumed at age 6 months. The period around 6 months was previously regarded as crucial because of the dramatic increase in childhood CD seen after the change of recommendations in infant feeding practices in Sweden.²⁰ In fact, the 3-day food records at 9 months of age show that a larger consumption of gluten is less likely to be followed by CD than a small amount (OR, 0.63; 95% CI, 0.19–2.05), although the findings are nonsignificant. Therefore, we are left with uncertainty whether quantity of gluten has a unidirectional effect on CD risk throughout infancy, or whether this risk changes over time.

The Kaplan-Meier curve (Figure 1)¹ also shows that the amount of gluten (low, medium, or high tertiles) does not influence the risk of CD in children younger than 24 months. Instead, the influence on CD onset is seen only later, primarily from the age of 4 years (with the median age at CD diagnosis occurring at 38 months). This is

important because it means that for the majority of children diagnosed with CD, the positive association with gluten intake was at 24 months (last record of measured gluten intake), potentially several years before serologic conversion. It is possible that gluten intake at 24 months exerts an influence on CD risk years later; it is also possible that it is merely a marker for subsequent gluten intake during ages 3 and 4 years (not measured in this study), which exerts a more immediate risk. This was not addressed in 2 earlier studies that involved giving small amounts of gluten between 4 and 6 months¹³ and restricting gluten until age 12 months.¹⁴

Of note, the strongest association between high gluten intake and later CD was seen at 12 months of age, suggesting that it may be at 1–2 years of age when parents should be “soft on gluten” rather than at 6–9 months, when most parents will seek recommendations on gluten amount.

Because the TEDDY group has previously shown that HLA DQ2 homozygosity is an important predictor for future CD, it is notable that the amount of gluten does not seem to interact with DQ2 status. It is also interesting that the risk of CD seems to be similar in children consuming low or moderate amounts of gluten. Only the highest tertile stands out. It would be helpful to see whether within the highest tertile there was a relationship with CD, so that those children exposed to very high amounts of gluten (eg, the highest centile) were at an even higher risk of CD. Although timing of gluten introduction has been studied previously (and appears to have no effect on CD risk), it would be worthwhile to explore whether timing or amount of gluten interacts with simultaneous infection to influence the risk of CD. On this subject, Swedish¹¹ and Norwegian²¹ data from cohort studies suggest that either timing¹¹ or total infectious disease burden²¹ could play a role in CD pathogenesis.

In summary, the well-designed infant nutrition study by Aronsson et al¹ points to the importance of the amount of gluten in infant nutrition for the risk of CD in Swedish children. It is slightly surprising that it is the amount from 1 year and onward that seems to be of greatest importance, and that the high consumers do not develop CD in the first 2 years of life but later. These findings need to be confirmed in other studies before changes in feeding recommendations in Sweden (between age 4 and 6 months, infants should be introduced to gradually increased amounts of gluten)²² and elsewhere are implemented. The authors should present the similar diet information from the TEDDY study involving children from lower risk countries such as the United States.

Whereas many of Hemingway’s books end with a tragedy, CD research seems to have a bright future. Since the discovery of the autoantigen in CD,²³ there has been a steady stream of research findings increasing our knowledge of this disease. Although Aronsson et al¹ offer only a small piece in the puzzle, the picture is nevertheless getting clearer and clearer.

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Conflicts of interest

The authors disclose no conflicts.

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