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COELIAC DISEASE

Does age at introduction to gluten affect risk of coeliac disease?

Two studies recently published in *The New England Journal of Medicine* have investigated whether the age at which an infant starts to eat gluten-containing foods affects their risk of developing coeliac disease. The findings of both studies suggest that the timing of when an infant starts to consume gluten has only a minor role in the development of coeliac disease.

"Coeliac disease is on the increase, with a multifaceted clinical appearance at any age," comments Markku Mäki, a leading researcher in the field of coeliac disease who was not involved in either study. Some evidence has suggested that the age at which gluten is introduced to the diet affects an infant's risk of developing coeliac disease. In many countries, these findings led to guidelines advising that gluten should not be introduced at <4 months of age or >7 months of age. However, the precise role that the age at which gluten is first consumed has in the risk of coeliac disease has remained controversial.

In the first study, 832 neonates with a first-degree relative who had coeliac disease were randomly assigned to start receiving dietary gluten when they were 6 months old (group A) or 12 months old (group B). Of these participants, 553 with a standard-risk HLA genotype or a high-risk HLA genotype completed the study. Coeliac disease autoimmunity was assessed at 15, 24 and 36 months and at 5, 8 and 10 years of age. Any participants with a positive serologic result underwent intestinal biopsies to determine whether they had coeliac disease.

When the participants were 2 years old, the incidence of coeliac disease autoimmunity and overt coeliac disease was much higher in group A than in group B. However, the difference was no longer statistically significant once the participants reached the age of 5 years. At the age of 10 years, participants with a high-risk genotype were more likely than those with a low-risk genotype to have developed coeliac disease autoimmunity. Other factors, such as the duration of breast-feeding and whether or not gluten was introduced while the infant was still breast-feeding were found to have no effect on the risk of coeliac disease.

Interestingly, of the participants who developed coeliac disease, those in group B developed the disease later than those in group A. This delayed development of coeliac disease could have beneficial effects on maintaining a good state of health during the critical periods of child development.

The second study included 944 infants who had high-risk genotypes (HLA-DQ2 or HLA-DQ8) and a first-degree relative with coeliac disease. The participants were randomly assigned to receive either 100 mg of immunologically active gluten daily ($n = 475$) or placebo ($n = 496$) from the ages of 16 weeks to 24 weeks. Serological measurements were taken periodically and the participants were followed up until they were at least 3 years old.

Coeliac disease was confirmed in 80 of the participants. However, the placebo and intervention groups had similar cumulative incidences of coeliac disease. The levels of coeliac disease autoimmunity at 3 years old were also similar between the two groups. In addition, the duration of breast-feeding (exclusive or not), did not affect the risk of coeliac disease, which is in agreement with the findings of the first study.

"Our results indicate that the early introduction of small quantities of gluten does not reduce the risk of coeliac disease at the age of 3 years in children with a genetic predisposition for the disease," say authors Sabine Vriezinga and Luisa Mearin. Furthermore, the authors suggest that although breast-feeding has many benefits for infants, it will not reduce their risk of coeliac disease, which needs to be clearly explained to parents.

The participants of this study are still being followed up, in order to assess the long-term effects of the intervention.

The researchers are also planning to carry out further work on many of the materials collected (such as serum samples, peripheral blood cells and small bowel biopsy samples) to improve understanding of how coeliac disease develops.

"Although the results of our study increase our knowledge of coeliac disease, we find ourselves at the beginning of research concerning prevention of the disease," conclude Vriezinga and Mearin. "The conceptual landscape of coeliac disease is, however, altered by our results and future research should explore other preventive strategies for this common disease."

"These well-designed studies show there is no window of opportunity at infancy for induction of oral tolerance by ingesting gluten or not," states Mäki. He suggests that the next step should be to solve the mystery of what is triggering the increase in autoimmune diseases such as coeliac disease.

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Original articles Lionetti, E. *et al.* Introduction of gluten, HLA status, and the risk of celiac disease in children. *N. Engl. J. Med.* doi:10.1056/NEJMoa1400697 | Vriezinga, S. L. *et al.* Randomized feeding intervention in infants at high risk for celiac disease. *N. Engl. J. Med.* doi:10.1056/NEJMoa1404172