Timing of Gluten Introduction and Islet Autoimmunity in Young Children: Updated Results From the BABYDIET Study

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Early introduction of gluten-containing food has been suspected to increase the risk of autoimmunity associated with type 1 diabetes and celiac disease (1–3). In an intervention study in which we randomized early and late first gluten exposure in children with high genetic risk for type 1 diabetes, we did not find a benefit in delaying gluten exposure with respect to autoimmunity associated with diabetes and celiac disease at age 3 years (4). Here, we report an update containing results from natural follow-up of up to 13 years.

In brief, 150 children younger than 3 months with at least one first-degree relative with type 1 diabetes and one of five specific type 1 diabetes–associated HLA genotypes were recruited between 2000 and 2006 and randomized to first exposure to dietary gluten at age 6 months or delayed until age 12 months. After inclusion, children were followed in 3-month intervals until the age of 3 years and yearly thereafter for efficacy (persistent islet autoantibodies) and safety assessment (4). Islet autoimmunity was defined as the development of persistent autoantibodies to one or more of the antigens insulin, GAD65, IA-2, and Zn-T8. Persistence was defined as being positive in at least two consecutive samples and in the last available sample. Celiac disease–related islet autoimmunity was defined as persistence of autoantibodies to transglutaminase C (TGCAs). Diabetes development was monitored and diagnosed according to the American Diabetes Association Expert Committee criteria (5). Data on duration of breast-feeding and introduction of gluten-containing food were taken from daily food records completed by the child's parents.

We compared groups based on both the intention-to-treat and the per-protocol principle, as 41 participants did not introduce gluten in the specified time interval according to their randomization group (19 earlier, 22 later). We further compared children by their true date of first exposure (4.5–7.5 compared with 10.5–13.5 months) or by using age at first gluten exposure (months) as a continuous variable. We used Cox regression to calculate hazard ratios for islet autoimmunity and type 1 diabetes with and without adjustment for duration of breast-feeding (0–3.0 vs. >3.0 months), breast-feeding at first gluten exposure (yes or no), age at first exposure to solid food (≤5.5 vs. >5.5 months), and number of days with gluten exposure in the 4 weeks after the first gluten exposure (≤13 vs. >13 days) as a dose variable. Statistical analyses were performed using SAS 9.3. The BABYDIET study was conducted at the Diabetes Research Institute (Munich, Germany) and approved by the ethics committee of the Ludwig-Maximilians University, Munich, Germany.

The median follow-up time in our data was 8.1 years (interquartile range 3.9–9.3 years). Overall, 27 children developed any islet autoantibodies, and of these, 17 developed multiple islet autoantibodies during follow-up. Fourteen children developed type 1 diabetes, and 22 developed TGCAs. We found no associations between any definition of exposure (intention to treat or per protocol) and any outcome in either unadjusted or adjusted analyses (Table 1). Relevant to the question of a potential benefit of delayed gluten introduction, hazard ratios comparing delayed exposure to standard exposure provided no suggestion of protection and were rather increased for islet autoantibody outcomes reaching a hazard ratio of 2.4 (95% CI 0.9–6.8) in the per-protocol analysis. This would be consistent with the findings from the Diabetes Autoimmunity Study in the Young (DAISY) (2). Gluten introduction while breast-feeding

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Table 1—Hazard ratios (95% CI) of development of islet autoantibodies (AAB), type 1 diabetes, and autoantibodies to TGCA for specific gluten exposure variables in the BABYDIET study, with and without adjustment for duration of breast-feeding, breast-feeding at first gluten exposure, age at first exposure to solid food, and number of days with gluten exposure in the 4 weeks after the first gluten exposure

Outcome	Outcome/exposed	Outcome/unexposed	Hazard ratio unadjusted	Hazard ratio adjusted
Late gluten exposure (intention to treat)				
Any islet AAB	15/73	12/77	1.4 (0.7−3.0)	1.4 (0.6−3.9)
Multiple islet AAB	9/73	8/77	1.2 (0.5−3.2)	1.3 (0.5−3.4)
Type 1 diabetes	8/73	6/77	1.3 (0.5−3.8)	1.5 (0.5−4.3)
TGCA	8/73	14/77	0.6 (0.2−1.4)	0.6 (0.2−1.4)
Gluten introduction 10.5–13.5 months compared with 4.5–7.5 months (per protocol)				
Any islet AAB	16/63	7/44	1.8 (0.7−4.3)	2.4 (0.9−6.8)
Multiple islet AAB	11/63	5/44	1.6 (0.6−4.6)	2.2 (0.7−7.2)
Type 1 diabetes	8/63	4/44	1.3 (0.4−4.4)	2.1 (0.5−8.4)
TGCA	7/63	9/44	0.5 (0.2−1.4)	0.6 (0.2−1.8)
Age at gluten introduction (per month later)				
Any islet AAB	—	—	1.1 (0.9−1.2)	1.1 (0.97−1.3)
Multiple islet AAB	—	—	1.1 (0.9−1.3)	1.2 (0.9−1.4)
Type 1 diabetes	—	—	1.1 (0.9−1.3)	1.1 (0.9−1.4)
TGCA	—	—	1.0 (0.8−1.1)	1.0 (0.8−1.1)

was not associated with any outcome. Results were similar if we restricted the intention-to-treat analyses to those 120 children who completed the follow-up until age 3 years in the original study (data not shown).

The follow-up findings of the BABYDIET study do not exclude that the age and manner that gluten is introduced into the diet of infants can affect the risk of type 1 diabetes. However, even with increased follow-up time and refined outcome definition, our data do not indicate that an intervention based on delayed gluten introduction over what is currently recommended in most countries will reduce the risk of developing autoimmunity related to type 1 diabetes. We cannot exclude potential benefits on the risk of celiac disease.

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