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 benefit in delaying gluten exposure with respect to diabetes and celiac disease associated autoimmunity 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 three 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 randomised to first exposure to dietary gluten at age 6 months or delayed until age 12 months. After inclusion, children were followed in three-monthly intervals until the age of three years and yearly thereafter for efficacy (persistent islet autoantibodies) and safety assessment (4, 5). 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 (6). Data on duration of breastfeeding 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 to 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 breastfeeding

(0–3.0 vs. >3.0 months), breastfeeding 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 DAISY study (2). Gluten introduction while breastfeeding 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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Author contributions

AB analyzed the data and wrote the first and final draft of the manuscript. RC, SH and CW were responsible for data acquisition and data quality, and contributed to the interpretation of the results and to the writing of the manuscript. AGZ and EB developed the study hypothesis and contributed to interpretation and writing. AGZ is the principal investigator of the BABYDIET study.

References

1. Norris JM, Barriga K, Hoffenberg EJ, Taki I, Miao D, Haas JE, et al. Risk of celiac disease autoimmunity and timing of gluten introduction in the diet of infants at increased risk of disease. JAMA. 2005;293(19):2343-51.

2. Norris JM, Barriga K, Klingensmith G, Hoffman M, Eisenbarth GS, Erlich HA, et al. Timing of initial cereal exposure in infancy and risk of islet autoimmunity. JAMA. 2003;290(13):1713-20.

3. Ziegler AG, Schmid S, Huber D, Hummel M, Bonifacio E. Early infant feeding and risk of developing type 1 diabetes-associated autoantibodies. JAMA. 2003;290(13):1721-8.

4. Hummel S, Pflüger M, Hummel M, Bonifacio E, Ziegler AG. Primary dietary intervention study to reduce the risk of islet autoimmunity in children at increased risk for type 1 diabetes: the BABYDIET study. Diabetes Care. 2011;34(6):1301-5.

5. Schmid S, Buuck D, Knopff A, Bonifacio E, Ziegler AG. BABYDIET, a feasibility study to prevent the appearance of islet autoantibodies in relatives of patients with Type 1 diabetes by delaying exposure to gluten. Diabetologia. 2004;47(6):1130-1.

6. Expert Committee on the Diagnosis Classification of Diabetes Mellitus. Report of the expert committee on the diagnosis and classification of diabetes mellitus. Diabetes Care. 2003;26 Suppl 1:S5-20.

Table 1. Hazard ratios [95% confidence intervals] of development of islet autoantibodies (AAB), type 1 diabetes and autoantibodies to transglutaminase C (TGCA) for specific gluten exposure variables in the BABYDIET study, with and without adjustment for duration of breastfeeding, breastfeeding 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 to 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]