

REVIEW ARTICLE

Infant Nutrition and Type 1 Diabetes

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SUMMARY

Introduction: Prospective studies on the development of type 1 diabetes show that islet cell autoimmunity begins early in life of affected individuals. Dietary factors are possible triggers or protective factors. **Methods:** Selective literature review and overview of current thinking on the role of nutrition in the etiology of type 1 diabetes. **Results:** Cohort studies have shown that children who were fed foods containing gluten before their fourth month of life were significantly more likely to develop anti islet cell antibodies. Prospective studies were unable to demonstrate any association between the early administration of cow's milk protein and islet autoantibodies. Vitamin D and fish oil supplements given in the first year may be protective. Interventional studies are currently examining the influence of a modified diet on the development of islet autoantibodies for infants with a genetic predisposition to type 1 diabetes. **Discussion:** Since diet is relatively easy to modify, it represents an opportunity for primary prevention. Current recommendations are to breastfeed babies exclusively for the first 4 to 6 months of life and introducing solids from 5 to 7 months.

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Key words: type 1 diabetes, infant nutrition, autoimmunity, primary prevention

Recent epidemiological and animal studies suggest that nutrition even in early childhood plays an important role in disease in later life (e1–e4). While the pathophysiological significance of obesity in the development of type 2 diabetes has long been established, there is currently discussion of a possible etiological or even protective role of nutritional factors in the pathogenesis of type 1 diabetes. The key pointers to the significance of the early years of life in respect of the initiation of the process of autoimmune beta cell destruction are found in prospective studies of type 1 diabetes. They suggest that children who go on to develop type 1 diabetes before puberty already have islet antibodies (islet ABs), a marker of autoimmune destruction, in the first two years of life (1–4). This suggests that the environmental triggers for the destruction process must be present in the first months of infancy. Possible triggers include infection and vaccination. However, a clear association has only been established between type 1 diabetes and congenital rubella; results for enteroviral infection are conflicting (e5). No specific vaccination-related associations have been able to be demonstrated in triggering autoimmune destruction (e5, e6). Similarly, the cited protective effect of BCG vaccination has not been confirmed, either in prospective observational studies or in case control studies (e7–e9). On the other hand, food-related antigens are among those to which the infantile immune system is exposed from the first months. Cow's milk and wheat proteins in particular have long been discussed as possible diabetogenic factors. Animal studies have shown that eliminating these proteins leads to a dramatic change in the incidence of autoimmune diabetes (5, e10). Epidemiological data support the supposition that nutritional factors such as breast milk, duration of breastfeeding and the time of introduction of supplementary food containing gluten, but also dietary vitamin D and fish oil, all influence type 1 diabetes incidence in predisposed children (6–9). This article offers an overview of current thinking surrounding nutritional influences on islet cell autoimmunity and type 1 diabetes, based on the authors' scientific experience and a selective review of the literature (*table*).

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Significance of the timing and type of supplementary food

Time of introduction of solids and duration of breastfeeding

Studies currently available on the timing of introduction of solid food, islet cell autoimmunity and type 1 diabetes are controversial. While two retrospective case control studies showed that children with type 1 diabetes received solid food significantly earlier than controls (16 ± 11 weeks versus 21 ± 14 weeks; p < 0.05, odds ratio [OR] 2.5; 95% confidence interval [CI] 1.4–4.3 for solids before 3 months) (e11, e12), other case control studies showed no such association (e13, e14). On the other hand, a retrospective case control study of 200 children diagnosed with type 1 diabetes under the age of 15 showed that children with type 1 diabetes received solid food significantly later than children in the control group (OR 0.4 [95% CI 0.2–1.0] for solids before six months) (e15).

TABLE

Nutritional factors in the etiology of type 1 diabetes (results of studies in man)*1

	Effect in fetal life	Effect in infancy/ childhood	Study design	References
Breast milk		-/0/+	CCS,CS	7, 24, e12, e14, e16, e45
Cow's milk		0/+	CCS, CS	7, 23, 24, e7–e9, e11, e45
Fish oil	-/0	-/0	CCS	8, 22
Gluten*2		0/+	CS	9, 10
Nitrate, nitrite, nitrosamine	+	0/+	CCS	22–24
Nicotinamide		-/0	IS	e43, e44
Vitamin C		-/0	CCS	23, e42
Vitamin D		-/0	CCS, CS	6, 17, 21
Vitamin E		-	CS	e41
Zinc		-/0	CCS	e39, e40

–, 0, +: indicate the effect of the relevant substance in the diet on the incidence of islet antibodies or type 1 diabetes;
 –: significantly protective effect;
 0: no association;
 +: significantly positive, disease promoting association;
 *1, studies with type 1 diabetes as an end point;
 *2, studies with islet antibodies as an end point;
 CCS: case control studies; CS, cohort studies; IS, intervention studies

The overall length of breastfeeding is also significant in this respect, since breastfed infants not only take in immunologically beneficial substances, but also receive solid food with its potentially detrimental components such as cow's milk or wheat proteins at a later stage. Because the gut has increased permeability for macromolecules in the early months of life, this is a key time for potential sensitization to food components. Increased permeability of the gut has been described in type 1 diabetes (e4). But discussion also surrounds the possibility that certain food substances such as gliadin, a protein fraction of gluten, adversely affects gut permeability by means of inflammatory reaction at the intestinal mucosa, thereby paving the way for other potentially damaging agents (e16)

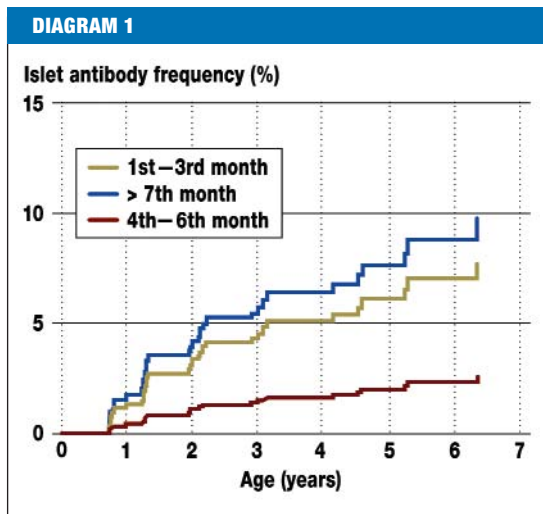
Prospective data on the significance of timing and type of supplementary food

Two prospective studies offer new, groundbreaking insights into the significance of the timing and type of supplementary feeding. Norris et al. (10) examined the relationship between the first time of feeding wheat products in supplementary feeding, and the development of islet cell autoimmunity, as part of the "Diabetes Autoimmunity Study in the Young" (DAISY) study. 1 183 children with a genetic predisposition for type 1 diabetes or first degree relatives with type 1 diabetes were recruited at birth and followed up to the age of four. Children receiving wheat products before the age of four months had a significantly increased risk of developing islet cell autoimmunity (hazard ratio [HR] 4.3; 95% CI 2.0–9.4), but so did those receiving wheat products for the first time after the sixth month of

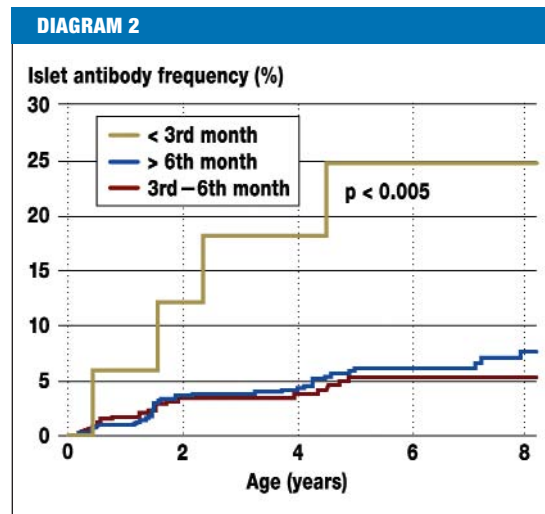
life (HR 5.4; 95% CI 2.1–13.8) (diagram 1). The German BABYDIAB study (9) is prospectively studying the development of islet cell autoimmunity in 1 610 children with at least one diabetic parent, recruited at birth. The BABYDIAB study found a significantly increased risk of islet cell autoimmunity in children who first received gluten containing products before the age of three months, compared with those who received cereals containing gluten for the first time between three and six months. (HR 5.2; 95% CI 1.7–15.5) (diagrams 2 and 3). By contrast with the data from the DAISY study, no significantly increased risk for gluten first exposure was found after the sixth month. The endpoint of this study was islet cell autoimmunity, not manifest type 1 diabetes. The incidence of multiple islet antibodies is, however, associated with manifest diabetes before puberty in nearly 100% of cases (2).

Gluten – pathologically significant beyond celiac disease?

Gluten is the precipitating antigen in celiac disease (e17) and is also suspected as a possible trigger of islet cell autoimmunity in type 1 diabetes (11). Celiac disease occurs with increased frequency both in type 1 diabetics and in children of type 1 diabetics, especially in the form of silent celiac disease, which is often diagnosed late (e18–e20). The association between type 1 diabetes and celiac disease is mediated by the common HLA haplotype DR3/DQ2, but also, it is thought, via comparable pathogenetic mechanisms, in particular defective immune regulation in the mucosa. Ventura et al. (12) studied the prevalence of other autoimmune diseases in relation to the duration of gluten exposure, in patients with celiac disease. Celiac disease patients had a significantly increased risk of other autoimmune diseases (14%), compared with healthy controls (2.8 %). The risk within the patient group increased with increasing delay in diagnosis of the celiac disease. Where celiac disease was diagnosed before the age of two, the prevalence of type 1 diabetes was 0.8 %, between the second and the tenth years, 4.7 %, and after the tenth year, 6.6 % (diagram 4).



Development of islet antibodies in relation to the timing of first administration of any cereal-based supplementary food, in the DAISY study (n=1 183 children); modified from Norris et al., JAMA 2003; 290: 1713–20.



Development of multiple islet cell antibodies in relation to the timing of first administration of gluten containing supplementary food in the German BABYDIAB study (n = 1 610 children; modified from Ziegler et al., JAMA 2003; 290: 1721–8.

On the basis of these findings it has been suggested that maintaining a gluten-free diet early on could reduce the incidence of other autoimmune diseases, in particular type 1 diabetes. It is as yet unclear which cereal subunit fraction is responsible for the initiation of the diabetes-specific autoimmune process. A strong antibody and T cell mediated response has recently been detected to the cereal storage protein Gli 1, which animal models have suggested may be significant.

Modulation of cereal proteins in early infant nutrition – primary prevention study BABYDIÄT

Building on the results of the BABYDIAB study described above, in which early feeding of gluten was shown to increase the risk of developing islet cell auto antibodies – the

BABYDIÄT study has now been running in Germany since 2001. The BABYDIÄT study seeks to delay or prevent the development of islet cell autoimmunity by delaying gluten exposure until the end of the first year of life. Infants under three months with first degree relatives with type 1 diabetes are recruited. Children in the intervention group receive a gluten-free diet until a year of age, while those in the control group receive gluten containing supplementary food from six months, in accordance with current German guidelines for infant nutrition (national breastfeeding council). The group is due to report for the first time in 2008.

Breast milk, breastfeeding and type 1 diabetes

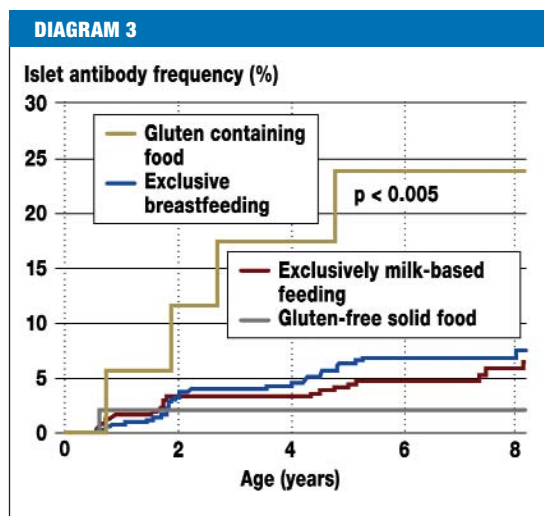
Protective effects of breastfeeding against diseases such as Crohn's disease (e22, e23), ulcerative colitis (e23), celiac disease (e24) and type 1 diabetes (7, 13) are described in the literature. The relationship between duration of breastfeeding and the incidence of islet cell antibodies was examined in 4 cohort studies. The German BABYDIAB study showed no significant association between duration of breastfeeding and the development of islet cell autoimmunity in early childhood (9, 14). This outcome agreed with results from the DAISY study from the USA (15) and the Australian BABYDIAB study (4). Only the Finnish DIPP study (Finnish Diabetes Prediction and Prevention Study) showed that a shorter duration of breastfeeding in genetically predisposed children was associated with a significantly increased risk of islet cell autoimmunity at the age of four. The duration of exclusive breastfeeding was a median of 0.2 months shorter in children with islet cell antibodies than in controls (e25).

Modulation of cow's milk protein in early infant nutrition – primary prevention study TRIGR

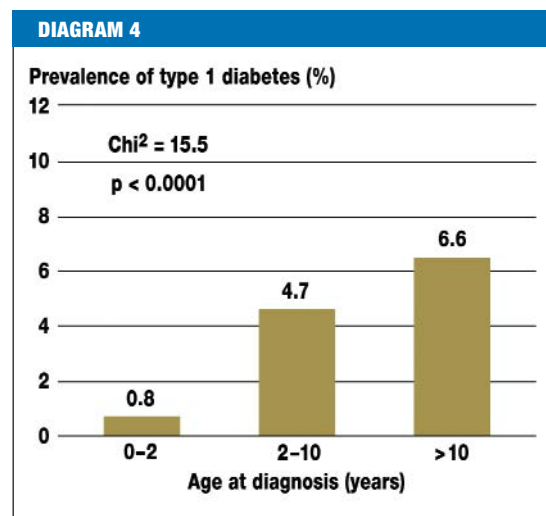
The extent to which cow's milk protein in infant nutrition plays a part in the development of islet cell autoimmunity and type 1 diabetes is currently under investigation in the international TRIGR trial (Trial to Reduce Diabetes in the Genetically at Risk). After weaning, children in the intervention group receive a special hydrolyzed food which no longer contains intact cow's milk protein, until six months of age. Control group children are fed a standard formula milk on the basis of cow's milk. A pilot study of 242 children for the TRIGR study showed that giving hydrolyzed food was associated with a significantly reduced cumulative incidence of islet cell antibodies. At the median observation period of 4.7 years, islet cell antibodies had been found in 13% of children in the intervention group, and 22 % of children in the control group (16).

Vitamin D as an immune modulator

Because of its immune modulating properties, vitamin D (1.25 dihydroxy cholecalciferol = calcitriol) is under discussion as a possible protective agent against diseases such as type 2 diabetes, multiple sclerosis, rheumatoid arthritis, inflammatory bowel disease, Addison's disease, Graves' disease and Hashimoto's thyroiditis (e26–e29). Saggese et al. (e30) showed that calcitriol is immunosuppressant in vitro, where it suppressed the proliferation of human lymphocytes and cytokine production. The identification of vitamin D receptors on almost all cells of the immune system, in particular on antigen presenting cells and activated T lymphocytes, supports the hypothesis that calcitriol may play a part as an immune modulator (e31). The results of the multicentre study EURODIAB showed that vitamin D supplementation in the first year of life was associated with a reduced risk of developing type 1 diabetes (odds ratio [OR] 0.7; 95% CI 0.5–0.9) (17). The question of the appropriate form and dose of vitamin D supplementation was not adequately addressed in this study. Finnish authors Hyppönen et al. (6) showed that the incidence of type 1 diabetes in individuals who received at least 2 000 IU vitamin D for the prevention of rickets in the first year of life was significantly reduced. The relative risk of developing type 1 diabetes with regular supplementation was 0.1 (95% CI 0.03–0.5), compared with those who received no vitamin D supplementation. In this cohort study, 10 821 children born in 1966 were followed up from birth to a year with data on the frequency of vitamin D administration, but with no data on harms arising from high dose vitamin D administration (such as nephrocalcinosis or hypercalcemia). However, native vitamin D levels are lower in this population than in central Europeans due to reduced exposure to sunlight (6). Vitamin D supplementation would therefore appear, according to current data, to be a promising



Development of islet antibodies in relation to the nature of supplementary food during the first three months of life, in the German BABYDIAB study (n = 1 610 children); modified from Ziegler et al., JAMA 2003; 290: 1721–8.



Prevalence of type 1 diabetes in relation to age at diagnosis of celiac disease (n = 909 patients); modified from Ventura et al., Gastroenterology 1999; 117: 297–303.

approach to the prevention of islet cell autoimmunity. The German pediatric society currently recommends continuous rickets prophylaxis throughout the first year of life of 10–12.5 μ g (400–500 IU) per day of Vitamin D. It is unclear whether this dose is sufficient to protect against the initiation of autoimmune processes.

Fatty acids from fish oil

Fish oil does not only contain vitamin D, but is also rich in long chain polyunsaturated fatty acids (PUFAs), in particular docosahexaenic acid (DHA) and eicosapentaenic acid (EPA). PUFAs are important components of the cell membrane, and therefore present in all tissues. PUFAs may by means of their anti-inflammatory activity have a modulating effect on the immune system of children at increased risk of type 1 diabetes (8). Currently of interest are a reduced expression of HLA class 2 alleles on activated human monocytes, and reduced expression of interleukin 1 β (e32–33). PUFAs play a key role in the synthesis of eicosanoids, and some studies show that children with type 1 diabetes show anomalies in prostaglandin metabolism (e34, e35). The neonate's supply of PUFA and vitamin D are dependent in the first instance on the mother during pregnancy (19, 20). Hence a Norwegian study investigated the influence of fish oil and vitamin D supplementation in pregnancy or during the first year of the child's postnatal life in type 1 diabetes risk (21). Children had a significantly reduced risk of type 1 diabetes where the mother took fish oil during pregnancy (OR 0.3; 95% CI 0.1–0.8). These data were shortly afterwards confirmed in a national case control study carried out by the same group (8).

Nitrates and nitrites

Dietary nitrates can be reduced in the gastrointestinal tract to nitrites and undergo further reaction to form toxic nitrosamines. In the first year of a child's life the most likely sources of nitrates are drinking water, used in the preparation of formula milk or in teas, or in vegetables and potatoes. N nitroso compounds have been shown in animal studies to be toxic to beta cells (e36, e37). It is also thought that nitrosamines reinforce the diabetogenic effect of certain viruses (e38). Epidemiological studies also point to a link between nitrate/nitrite consumption and the incidence of type 1 diabetes (22, 23, 25). A Swedish case control study of 867 children found an association between increased risk of type 1 diabetes and a diet rich in nitrates, nitrites or nitrosamines (RR 2.4 and 4.4 respectively) (23). This result was not confirmed, however, by an Australian study, which found no increased risk of type 1 diabetes in children with high dietary intakes of nitrosamines (24). On the other hand a Colorado-based study of 1 280 children under 18 which developed type 1 diabetes between 1978 and 1988 found only a weak correlation between nitrate levels in drinking water and type 1 diabetes incidence (25).

Perspectives – recommendations for infant nutrition

No adequately robust data currently exist to support specific nutritional recommendations for children at increased risk of type 1 diabetes. Dietary modification with a view to prevention of type 1 diabetes should only be instigated in the context of studies with regular follow-up. Definite dietary recommendations must await robust evidence which identify dietary factors which are clearly associated with increased and/or decreased risk of type 1 diabetes. Until then, the recommendation remains that infants should be breastfed for the first four to six months, with the introduction of solid food at the age of five to seven months.

Conflict of interest statement

The authors declare that no conflict of interest exists according to the Guidelines of the International Committee of Medical Journal Editors.

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