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Infant Feeding and Timing of Complementary Foods in the Development of Type 1 Diabetes

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Abstract

Type 1 diabetes (T1D) is an autoimmune disease that results from the destruction of the β cells of the pancreas in genetically at-risk individuals. The autoimmune process that precedes the development of T1D is believed to be triggered by environmental factors, including nutrition. Early introduction of complementary foods has been implicated in the etiology of T1D as a possible explanation of the increasing incidence of the disease, particularly in children younger than 5 years of age. Infant feeding recommendations have been designed to promote adequate growth, provide essential nutrients, and reduce the risk of developing chronic illnesses. The World Health Organization and the American Academy of Pediatrics recommend exclusive breastfeeding to 6 months of age followed by continued breastfeeding as complementary foods are introduced. A lack of compliance with these recommendations has been observed in the general population as well as in infants at high risk for T1D. Dietary factors such as the provision of breast milk and duration of breastfeeding, the age at introduction of cow's milk and gluten-containing foods, as well as other complementary feeding have been investigated. However, the evidence that early infant feeding patterns are linked with T1D currently remains inconclusive.

Keywords

Type 1 diabetes; Autoimmunity; Infant feeding; Breastfeeding; Nutrition

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Compliance with Ethics Guidelines

Conflict of Interest Anita M. Nucci, Suvi M. Virtanen, and Dorothy J. Becker declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Introduction

The incidence of type 1 diabetes (T1D) in children and young adults is increasing in most developed countries and is predicted to continue to increase in the future [1]. There is increasing evidence that the pathogenesis of T1D is likely to be a result of a combination of genetic predisposition and environmental or lifestyle risk factors. Environmental triggers believed to influence the expression of the disease include viruses such as Coxsackie B, growth and/or obesity, and nutritional factors including cow's milk proteins, cereals, *n*-3 fatty acids, and vitamin D [2]. Exclusive breastfeeding for at least 6 months with continued breastfeeding as complimentary foods are introduced has been recommended for healthy growth and development of all infants. Evidence linking early infant feeding practices with the development of T1D is inconclusive. Although unproven, avoidance of the introduction of complementary foods earlier than 6 months of age has also been suggested to reduce the risk of T1D and other chronic diseases in childhood.

The autoimmune process that leads to the destruction of the β cells of the pancreas and the development of T1D is believed to begin during infancy as islet autoantibodies can appear within the first 2 years [3]. The rise in incidence of the disease has been reported to be associated with a shift to younger ages [4] and increasing most rapidly in children less than 5 years of age [1]. However, recent reports from the US population have not observed this latter finding [5, 6]. There are new intriguing data suggesting that nutritional and other factors may affect the immune system via alterations of the microbiome [7•]. Mode of birth (vaginal vs. cesarean section) and infant feeding (human milk vs. infant formula) affect the development of gut microbiota. Although the study populations have been small, the gut microbiota in children with β-cell autoimmunity or T1D has been found to have a lower diversity than in healthy age-matched controls [8]. In this review, feeding recommendations and patterns across continents will be summarized followed by a discussion of the recent evidence regarding the associations between nutritional factors proposed to protect or predispose to the development of β-cell autoimmunity and T1D in humans.

Infant Feeding Recommendations and Practices

Feeding Recommendations

Although international infant feeding recommendations do not vary widely, infant feeding patterns differ between countries due to socio-demographic factors such as parental education and age, and cultural differences in food habits [9–13]. The World Health Organization (WHO) and American Academy of Pediatrics (AAP) recommend exclusive breastfeeding for the first 6 months of life followed by continued breastfeeding as complementary foods are introduced [14–16]. The WHO and AAP also recommend that breastfeeding continue for the remainder of the first year of life or longer as desired by the mother and infant. These recommendations are based on the reduced risk of disease development that has been observed in breastfed infants, including acute otitis media, non-specific gastroenteritis, and severe lower respiratory tract infections [17]. Complementary foods are recommended to be sufficient in energy, protein, and micronutrients, including iron, and to be introduced beginning at approximately 6 months of age. Introduction of complementary foods prior to this age is not recommended as they may displace breast milk

consumption [16]. However, after 6 months of age, breast milk alone may not be sufficient to meet all nutritional requirements. The WHO and AAP have not given specific recommendations for the order in which complementary foods are to be introduced. Whole cow's milk is not recommended as the primary milk feeding before 12 months of age because of the high solute density, and it does not contain sufficient iron to meet requirements [14, 15].

In contrast to the strong association between breastfeeding and reduced risk of several acute infectious illnesses, the evidence that early infant feeding patterns are linked with chronic childhood diseases, such as asthma, allergies, and T1D, is inconsistent [18–23]. Observational studies have found that early introduction of more than four complementary foods (<4 months of age) is associated with an increased risk of atopic dermatitis [24]. The European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) recommends that complementary foods be introduced after 4 months of age but before 6 months [25]. In addition, ESPGHAN recommends that foods containing gluten be introduced gradually while the infant is still being breastfed and that gluten not be introduced early or late (≥7 months of age) to reduce the risk of celiac disease, T1D, and wheat allergy. This evidence was based on studies with small numbers of outcomes [22, 26] and has later been questioned in regard to celiac disease [27] and T1D autoimmunity [28] as well as atopic sensitization to wheat [29].

Feeding Patterns

Previous studies have shown that women with T1D are less likely to breastfeed their infants or breastfeed for a shorter length of time than women without T1D [30–32]. In the BABYDIAB and BABYDIET study cohorts of infants with a first-degree relative with T1D, fewer infants who had a mother with T1D were breastfed during the first year of life than those who had a mother without T1D (77 vs. 86 %, respectively) [31]. In a large population of infants with a familial and genetic risk for T1D who participated in the Trial to Reduce Insulin-dependent diabetes mellitus in the Genetically at Risk (TRIGR) study (n=2159), exclusive breastfeeding was found to be less frequent among mothers with vs. without T1D at 1, 4, and 6 months of age (14.3 vs. 43 %, 7.6 vs. 24.2 %, and 1.4 vs. 3.4 %; respectively) [32]. However, after adjustment for potential confounding factors (mode of delivery, gestational age, maternal age and education), maternal T1D status was not independently associated with shorter duration of breastfeeding in this population. In the Finnish Type 1 Diabetes Prediction and Prevention (DIPP) project, longer duration of breastfeeding was found to also be associated with more years of parental education and older maternal age in these genetically at-risk infants [33].

Although the duration of breastfeeding in mothers with T1D has been found to be shorter than in unaffected mothers, breastfeeding initiation rates for infants at risk for T1D appear to meet or exceed those found in the general population. Worldwide breastfeeding initiation rates have been reported to range from 91 to 97 % in Australia [34], 74 to 99.5 % in Europe, 69 to 83 % (average 73 %) in Canada, and 27 to 69.5 % in the USA [35, 36]. In The international Environmental Determinants of Diabetes in the Young (TEDDY) study (n=7026), the rates of breastfeeding initiation were 96 % in infants of mothers with T1D and

98 % in infants with a father or sibling with T1D [13]. However, the duration of exclusive breastfeeding as recommended by the WHO and AAP was met by <20 % of the infants at high risk for T1D in these research populations [13, 32, 33, 37].

Results from the US Feeding Infants and Toddler Study have shown that two thirds of infants in the general population had been fed complementary foods between 4 and 6 months of age [38]. Feeding patterns in 12 European countries were compared as part of the Euro-Growth study, and at age 5 months, 95 % of infants had been fed solid foods [39]. Similar findings have been reported in populations of infants at increased genetic risk for T1D. The median age of exposure to solid foods in infants in the BABYDIET cohort was earlier in those who had a mother with vs. without T1D (5.5 and 5.9 months, respectively) [37]. In the Finnish DIPP study cohort, infants were introduced to complementary foods at the median age of 3.5 months (range, 1 to 6 months) [33]. In the TEDDY study, the introduction of cow's milk (including cow's milk-based infant formulas) occurred earliest in infants of mothers with T1D and gestational diabetes followed by infants with a father and/or sibling with T1D and latest in infants without a family member with diabetes [13]. In contrast, gluten-containing foods were introduced later in TEDDY infants with a parent and/or sibling with T1D (median age 6 months) compared to infants without diabetes in the family (median age 5 months). These data indicate low adherence to the current recommendations for the introduction of complementary foods in both a high-risk and the general population.

Dietary Mechanisms of Action

Multiple mechanisms of action have been proposed to explain the possible associations between infant diet and the risk of developing islet autoimmunity and T1D [2, 21]. Infant diet may be involved in the initiation of autoimmune process by the introduction of an antigen that cross-reacts with islet cell antigens [40]. Elevated levels of antibodies to cow's milk protein have been found in children with newly diagnosed T1D [23]. This finding may be due to increased exposure to cow's milk, increased reactivity to cow's milk proteins, or increased intestinal permeability to cow's milk proteins [41]. Although there is no clear proof that breastfeeding is protective, it is thought to protect against the development of T1D as breast milk contains antibodies (secretory immunoglobulin A) which enhance the infant's immune response and increases β-cell proliferation while also delaying the introduction of food antigens [2]. Young children who present with early signs of β-cell autoimmunity also often have insulin autoantibodies. Increased levels of IgG-antibodies binding to bovine insulin have been found at 3 months of age in infants who were exposed to cow's milk formula vs. infants who were exclusively breastfed [42]. The authors postulate that this immune response may lead to an autoimmune targeting of human insulin and insulin-producing β cells of the pancreas with subsequent development of T1D.

There is increasing recent research interest in the role of the intestinal microbiome, which is affected by diet and antibiotic exposures beginning early in life. It is suggested that the microbiome modulates intestinal homeostasis, and variations are related to the risk of developing metabolic illnesses [43]. Based on some data in rodent TID, the DIPP investigators examined the role of the intestinal microbiome by examining prediabetic stool

samples of four children who progressed to T1D and four matched autoantibody negative controls. The stool samples were analyzed before and at seroconversion to autoantibody positivity and again near the time of diagnosis of T1D in the cases and at corresponding ages in the control children [44]. The study showed that the cases developed a microbiome that was less diverse and stable than that seen in the healthy controls. Another recent study of 33 infants genetically predisposed to T1D reported a marked drop in alpha-diversity of the microbiome in those who progressed to T1D between the time of seroconversion and T1D diagnosis that was accompanied by spikes in inflammation-favoring organisms, gene functions, and serum and stool metabolites [7]. These studies suggested that changes in the intestinal microbiome may be the result of the etiologic process, specifically the progression from islet autoimmunity to T1D. This burgeoning area of research is evaluating relationships between diet and diversity of the microbiome and the possibility that progression of autoimmune diseases such as T1D could be affected by manipulation of intestinal bacteria composition.

Associations Between Infant Diet and Autoimmunity

Four large cohort studies have examined the relationship between early infant feeding and the risk of developing diabetes-associated autoantibodies. The BABYDIAB study included 1610 children in Germany with at least one parent with T1D who were followed until 8 years of age [22]. Study measures included dietary interviews to determine the duration of exclusive and any breastfeeding, the timing of introduction of milk-based and solid foods, and blood samples to determine the presence of islet autoantibodies (insulin, glutamic acid decarboxylase (GAD), or insulinoma antigen-2 (IA2) antibodies). In the 85 children who developed islet autoantibodies, there was no association between the risk of developing autoantibodies and duration of total or exclusive breastfeeding. However, children who received gluten-containing foods prior to 3 months of age had an increased risk for positivity for at least one autoantibody compared to children who had been exclusively breastfed. No increased risk for the development of islet autoantibodies was found in children who initially received gluten-containing foods after 6 months of age. The Diabetes Autoimmunity Study in the Young (DAISY) is an ongoing longitudinal observational study that is examining the interaction between genetic and environmental factors on the development of islet autoimmunity and T1D in the US children who are at genetic or familial risk for the disease [26]. Of 1183 children enrolled, only 34 had islet autoimmunity. The researchers reported that children initially exposed to cereals early (birth to 3 months of age) and late (≥7 months) had an increased risk of islet autoimmunity after adjustment for human leukocyte antigen (HLA) genotype, family history of T1D, ethnicity, and maternal age. Thus, these two studies of relatively small numbers of children with islet autoimmunity reported somewhat different results.

In the DIPP study, Virtanen et al. examined the age of introduction of new foods and β-cell autoimmunity in Finnish children (n=3565) with genetic susceptibility to T1D [20]. In addition to dietary interviews conducted at 3, 6, 12, and 24 months of age, the families completed at home a follow-up form to assess use of breast milk and/or infant formula, type of formula used (intact cow's milk protein, hydrolyzed cow's milk protein, soy protein), and the age of introduction of solid foods. Solid foods and liquids were categorized as follows:

fruits and berries, roots (potato, carrot, turnip, swede), cereals (wheat, rye, oats, and barley), other cereals (maize, rice, millet, buckwheat), cabbage, milk products and foods containing milk, cow's milk-based infant formulas (excluding hydrolyzed and soy formulas), fish, meat, and sausage. Wheat, rye, oats, and barley were also analyzed separately. Advanced β-cell autoimmunity (repeated positivity for islet cell antibodies plus at least one other antibody endpoint) developed in 111 children. No associations were found between the duration of total breastfeeding, exclusive breastfeeding or the age of exposure to cow's milk products (including cow's milk-based infant formulas) or cereals and the risk of developing islet autoimmunity. However, introduction of fruits and berries at ≤4 months of age (vs. later exposure) and roots at 3–3.99 months of age (vs. later) were associated with increased risk. Virtanen et al. more recently re-examined the associations between age at the introduction of foods during infancy and islet autoimmunity in the DIPP cohort (n=6069) with larger numbers of outcomes (n=265) and found the early introduction of root vegetables (<4 months of age) was associated with the increased risk of developing advanced β-cell autoimmunity independent of the introduction of other foods and socio-demographic and perinatal putative confounding factors [28].

In BABYDIET, young children (<2 months of age; n=150) from Germany who had not been exposed to gluten, and had at least two first-degree relatives with T1D or at least one first-degree relative with a high-risk T1D HLA genotype, were randomized to be introduced to gluten at 6 months of age (control group) or 12 months of age (late introduction) [45]. The researchers found that delaying gluten exposure until the age of 12 months did not reduce the prevalence of islet autoimmunity in children genetically at risk for T1D using both per protocol and intention to treat analyses (n=24).

The TRIGR study is an international randomized double-blind trial that assigned infants with HLA-conferred susceptibility to T1D and at least one first-degree family member with T1D to receive either a casein hydrolysate formula or a standard cow's milk-based formula (control group) after weaning from breast milk during the first 6 to 8 months of life. The TRIGR pilot study conducted in Finland (n=230) between 1995 and 1997 found a decrease in the risk of seroconversion to positivity for one or more autoantibodies in the casein hydrolysate group after adjustment for age of introduction and duration of formula exposure [46]. However, in the TRIGR trial, the largest newborn intervention study which was conducted in three continents (15 countries), no significant difference in the absolute risk of positivity for two or more islet autoantibodies was found between the casein hydrolysate (n=1081) and conventional formula (n=1078) groups (13.4 vs. 11.4 %, respectively) after 7 years of follow-up [47••]. The TRIGR study population will be followed until 2017 when the last child enrolled reaches 10 years of age to determine if weaning to a casein hydrolysate formula has an effect on the risk of developing clinical T1D.

Associations Between Infant Diet and Type 1 Diabetes

Multiple studies have investigated the relationship between infant feeding and the development of T1D. In German children who were diagnosed with T1D at less than 5 years of age (n=760) with age, gender, and residence-matched controls, evaluation of infant diet revealed that the overall duration of breastfeeding and age at introduction of cow's milk-

based infant formulas and solid foods, and current cow's milk intake were inversely related to the risk of developing T1D [21] supporting earlier case-control findings [48]. The authors reported a linear trend (dose-response) relationship between the variables. In a population-based cohort of Finnish children (n=6209) followed prospectively to examine the effect of complementary feeding on the development of cow's milk allergy, Savilahti and Saarinen reported that exposure to cow's milk-based infant formula at the maternity hospital was not associated with the development of T1D (n=45) [23]. In the DAISY study, 53 of 1835 babies at increased genetic risk for T1D developed the disease. The researchers reported that early (<4 months) exposure to fruit (excluding fruit juice) and late (≥6 months) exposure to foods containing rice/oats predicted the development of T1D, after adjustment for HLA, first-degree relative with T1D, maternal education, and delivery type [49]. Children who were being breastfed when wheat and barley were introduced had a lower risk for T1D than those who were not breastfed at that time. Age at first exposure to cow's milk (including cow's milk-based infant formula) and the duration of breastfeeding (including exclusive breastfeeding) were not predictive of T1D.

The SEARCH Nutrition Ancillary Study (SNAS) examined the relationship between the retrospective reported timing of complementary food introduction and age at diagnosis of T1D in the US SEARCH for Diabetes in the Youth study population (n=1077) [50]. The introduction of sugar-sweetened beverages (excluding fruit juice) in the first year of life was associated with a 5-month earlier age at diagnosis after adjustment for gender, race, education, income, birth year, breastfeeding status, HLA risk status, and maternal diabetes. After stratification by genetic predisposition to T1D, consumption of fruit juice before 12 months of age was associated with a younger age at diagnosis in those with a high-risk HLA genotype. The above studies with differing designs and numbers do not provide consistent associations between infant feeding and the development of T1D.

Conclusion

Exclusive breastfeeding is recommended for at least 6 months of age with continued breastfeeding as complimentary foods are introduced. Evidence linking early infant feeding practices with T1D is inconsistent and remains inconclusive. Infant feeding recommendations beyond those required for healthy growth and development have been issued by ESPGHAN to reduce the risk of T1D, celiac disease, and wheat allergy. The society recommends that complementary foods be introduced between 4 to 6 months of age and that gluten-containing foods be introduced while the infant is still being breastfed (between 4 to 7 months of age). The feeding pattern data from the very large international TRIGR trial may reveal relationships between infant diet and development of autoimmunity and progression to T1D in a very high-risk population of children. The TEDDY study along with other ongoing large cohort studies such as DIPP and DAISY will further assess the role of viruses, nutrition, psychosocial factors, and other environmental agents on the risk of developing T1D, alone or in combination, in genetically susceptible children. The intriguing questions of whether diet affects the onset of T1D autoimmunity or progression to diabetes do not yet have definitive answers.

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