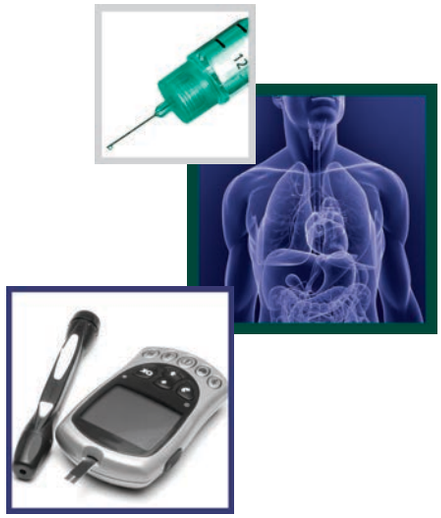
MANAGEMENT PERSPECTIVE

Early introduction of complementary foods: is there a link with Type 1 diabetes?



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Practice Points

- Complementary feeding starts earlier than recommended in many developed countries and is associated with sociodemographic and lifestyle factors.
- Early introduction of cow's milk products have been suspected to increase the risk of Type 1 diabetes (T1D), although the evidence is inconclusive.
- Early introduction of solid foods, such as cereals or root vegetables, may be associated with an increased risk of T1D.
- The observed associations between early infant feeding and development of T1D could be due to confounding by socioeconomic and lifestyle factors.
- Early introduction of cow's milk may increase gut permeability or initiate immunization to bovine insulin, which may lead to autoimmune responses to human insulin and β-cells.
- Toxins in root vegetables or added ingredients in baby foods could play a role in the development of T1D.
- Current recommendations to exclusively breast-feed infants up to the age of 4–6 months and to then continue breastfeeding together with complementary feeding up to the age of 1–2 years are also supported by current knowledge of the etiology of T1D.

SUMMARY Early introduction of complementary foods has been demonstrated to play a role in the development of clinical and preclinical Type 1 diabetes. The evidence on the association of early introduction of cow's milk with an increased risk of Type 1 diabetes is contradictory. Case–control studies indicate a positive association, while associations have mainly not been observed in more reliable cohort studies. Early introduction of solid foods, such as cereals and root vegetables, including potatoes, seems to be associated with an increased risk of early or advanced preclinical Type 1 diabetes.

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The autoimmune process leading to clinical Type 1 diabetes (T1D) may start in early infancy. The destruction of pancreatic β-cells is believed to be mediated by autoreactive T cells [1]. Diabetes-associated autoantibodies are the first indicators of such a process, which has turned out to have a highly variable duration. Islet cell antibodies, insulin autoantibodies, and antibodies to glutamic acid decarboxylase and tyrosine phosphatase-like protein have been confirmed to predict progression to clinical T1D. The higher the number of autoantibodies detected, the greater the likelihood of developing overt disease [2]. The presence of one autoantibody is classified as early prediabetes, two autoantibodies as advanced prediabetes and three or more autoantibodies as late prediabetes. More than half of children with advanced or late prediabetes are likely to develop clinical T1D during subsequent years [3].

T1D has a polygenic background, but the most important risk genes are located within the HLA class II region [4]. For example, the risk of developing T1D among Finnish children is estimated to be 8% for the high-risk *HLA-DQB1* genotype and 2% for the moderate risk *HLA-DQB1* genotype, compared with the average population risk of 0.7% [5].

Several dietary factors during pregnancy, infancy and childhood have been linked to the development of clinical or preclinical T1D (pre-T1D) in the child [6–9]. Breastfeeding, zinc, vitamins C, D and E, and n-3 fatty acids have been reported as potentially protective against T1D, whereas *N*-nitroso compounds, cow's milk, increased linear growth and obesity may increase the risk [6,8,10]. Most research attention has been paid so far to early infant feeding patterns.

As the incidence of T1D is increasing most rapidly among children younger than 5 years of age in many high- and middle-income countries [11], there is increasing interest in the impact of early exposures such as infant diet on the development of the disease. This article summarizes the current knowledge on the significance of early complementary feeding on the development of T1D. The term complementary feeding includes both infant formula and solid foods, and exclusive breastfeeding refers to the period when the infant receives only breast milk, water and/or vitamin and mineral supplements.

Age at introduction of complementary feeding

The order and timing according to which complementary foods are introduced to the infant differ largely by culture and region. For example, in North America, cereals are often given as the first complementary food after infant formula [12,13], whereas in Finland the first complementary feeding after infant formula comprises potatoes and carrots [14]. Currently, in many developed countries, complementary feeding starts early in relation to the recommendations, which suggest that exclusive breastfeeding should be continued until the age of 4–6 months or 6 months [15–17,101].

According to a recent systematic review, determinants of early introduction of complementary foods are young maternal age, low maternal education, low socioeconomic status, absence or short duration of breastfeeding, maternal smoking, and lack of information or advice from healthcare providers [18]. Additionally, single marital status of the mother, urban environment, having a first baby, smoking and having a baby of male sex predict a shorter duration of total and exclusive breastfeeding [19,20].

Early infant diet & development of T1D

In an ecological comparison study in which breastfeeding rates and incidence of T1D were analyzed in several countries, the frequency of breastfed children at the age of 3 months was inversely associated with T1D [21]. On the other hand, breastfeeding frequency during the past 20 years was not related to the disease incidence in a Swedish analysis [22]. Ecological correlation studies do not include information on the different individuals, so potential confounding factors cannot be readily controlled, and methods of measurement may vary between countries. Therefore, ecological studies are prone to several errors and should be regarded mainly as hypothesis-generating studies.

Several case–control studies have evaluated the associations between overall and/or exclusive breastfeeding and the risk of clinical T1D, but the findings remain inconsistent [6,8]. In a meta-analysis of case–control studies available in 1993, Gerstein showed that short breastfeeding duration (<3 months) was related to an increased risk of T1D with an odds ratio of 1.43 [23]. The results of the meta-analysis were similar whether it was based on 12 relevant studies, or on the four that met the methodological

criteria designed to ensure that a representative proportion of all incident cases were included, that the possibility of bias in the selection of control subjects was minimized, that the control and case subjects came from the same population, and that an equally reliable infant feeding history was available. However, the long-term maternal recall and differences in participation rates between case and control subjects may have biased the results of case–control studies [24]. An inverse association has been observed between age at introduction of cow's milk products and the risk of T1D in some [25]; although not in all studies [26]. The meta-analysis of case–control studies implied that an early exposure to cow's milk (<4 months of age) is a risk factor of T1D (odds ratio: 1.63) [23]. Early exposure to cow's milk is related to a shorter duration of exclusive and overall breastfeeding. When the effects of the duration of breastfeeding and age at introduction of cow's milk were studied at the same time in a Finnish national case–control study, only early introduction of cow's milk was significantly related to the risk of T1D [27]. Increased weight gain did not explain this association [28].

Prospective cohort studies following individuals with increased genetic susceptibility to T1D **(Table 1)** have mostly not found any association between duration of either overall or exclusive breastfeeding or early age at introduction of cow's milk and development of early [13,29,30] or advanced pre-T1D [14]. In a Swedish population-based cohort, shorter exclusive or overall breastfeeding (<4 months) as well as early exposure to cow's milk-based infant formula (<4 months of age) were related to greater risk of early β-cell autoimmunity [31].

Introducing gluten-containing cereals early (<3 months of age) was associated with early pre-T1D in a German cohort of first-degree family members of subjects with T1D [30], whereas in a Colorado (USA) cohort consisting of children with familial T1D and those with an increased HLA-conferred risk, both early (<4 months of age) and later (>6 months of age) introduction of cereals, compared with introduction at 4–6 months of age, was related to a higher risk of early pre-T1D **(Table 2)** [13]. In the Colorado study, this association was seen for any gluten-containing or rice cereals. According to Finnish observations from a cohort of children with increased HLA-conferred risk of T1D, early introduction of root vegetables including potatoes is associated with advanced pre-T1D; this association was not attributable to putative sociodemographic, perinatal or dietary confounding factors [14]. In the Finnish study, early age at introduction of wheat, rye, oats and barley cereals, and egg was also related to the risk of advanced pre-T1D, but only during the first 3 years of life, and these associations disappeared when age at introduction of root vegetables was taken into account. Of note, studies that have reported and analyzed the age at introduction of several foods at the same time in relation to pre-T1D are scarce [14,32]. The indication of different foods as dietary risk factors for T1D in Finland versus the USA and Germany may be related to the differences in infant feeding habits, carrots and potatoes being the most popular weaning foods in Finland.

The only intervention trial available so far is the pilot study TRIGR [8,33]. TRIGR is designed to test whether weaning to an extensively hydrolyzed formula instead of a traditional cow's milk-based formula after the breastfeeding period will decrease the risk of T1D [102]. The findings from the pilot study suggest that the emergence of β-cell autoimmunity can be reduced by approximately 50% by the age of 10 years by using an extensively hydrolyzed casein-based formula instead of a regular cow's milk-based one during the first 6–8 months of life. When the presence of autoantibodies was assessed, the group found that 17 in the treatment group versus 33 in the control group had at least one autoantibody, and eight versus 17 had two or more autoantibodies [8]. Intention-to-treat principle was used for the analyses. These children had a very high risk of T1D: they had both a first-degree relative with T1D and an increased HLA-conferred disease risk. It is noteworthy that TRIGR compared an extensively hydrolyzed casein formula to a cow's milk-based one. Such a comparison is not possible in the available observational studies.

Potential mechanisms & explanations for the associations between early infant feeding & the development of T1D

Dietary exposures can act as proxies of other life style characteristics, and the observed associations between dietary factors and T1D may result from confounding variables. Perinatal factors such as older maternal age, higher birth weight, lower gestational age, lower birth order and cesarean section may be risk factors for T1D, although the findings remain inconsistent [34–36]. Findings regarding the putative effects

Table 1. Prospective cohort studies evaluating the association of total and exclusive breastfeeding and the introduction of cow's milk with the risk of preclinical Type 1 diabetes.

Study (year)	Risk of T1D	Subjects (n)	Follow-up time (range)	End point	End points reached (n)	Outcome	Ref.
Exclusive breastfeeding							
Couper *et al.* (1999)	First-degree relative with T1D	317	Mean: 29 months (4–73 months)	Early pre-T1D	18–52	–	[29]
				Advanced pre-T1D	22	–	
Ziegler *et al.* (2003)	Parent with T1D	1610	Mean: 6.5 years (9 months to 12.5 years)	Early pre-T1D	85	–	[30]
Holmberg *et al.* (2007)	General population	3788	5 years	Early pre-T1D	18–197	↓	[31]
Virtanen *et al.* (2011)	Genetic risk	6069	4.9 years (0.2–11.1 years)	Advanced pre-T1D	265	–	[14]
Total breastfeeding							
Couper *et al.* (1999)	First-degree relative with T1D	317	Mean: 29 months (4–73 months)	Early pre-T1D	18–52	–	[29]
				Advanced pre-T1D	22	–	
Norris *et al.* (2003)	Genetic risk or first-degree relative with T1D	1183	Median: 4 years (9 months to 9 years)	Early pre-T1D	34	–	[13]
Ziegler *et al.* (2003)	Parent with T1D	1610	Mean: 6.5 years (9 months to 12.5 years)	Early pre-T1D	85	–	[30]
Holmberg *et al.* (2007)	General population	3788	5 years	Early pre-T1D	51–219	↓	[31]
Virtanen *et al.* (2011)	Genetic risk	6069	4.9 years (0.2–11.1 years)	Advanced pre-T1D	265	–	[14]
Introduction of cow's milk							
Couper *et al.* (1999)	First-degree relative with T1D	317	Mean: 29 months (4–73 months)	Early pre-T1D	18–52	–	[29]
				Advanced pre-T1D	22	–	
Norris *et al.* (2003)	Genetic risk or first-degree relative with T1D	1183	Median: 4 years (9 months to 9 years)	Early pre-T1D	34	–	[13]
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Holmberg *et al.* (2007)	General population	3788	5 years	Early pre-T1D		↑	[31]
Virtanen *et al.* (2011)	Genetic risk	6069	4.9 years (0.2–11.1 years)	Advanced pre-T1D	265	–	[14]

–: No association; ↓: Decreased risk; ↑: Increased risk; Pre-T1D: Preclinical Type 1 diabetes; T1D: Type 1 diabetes.

of socioeconomic status, parental education, place of residence and maternal smoking during pregnancy on the development of T1D are controversial [14,35,37,38]. Adjustment for putative confounding sociodemographic, perinatal and dietary factors have been applied only in a few studies investigating the associations between early feeding and the development of T1D. However, the effects of the adjustment on the results have been minor [14].

Early introduction of cow's milk or solid foods to an infant's diet may be a true risk factor for T1D, reflecting a causal relationship. Early introduction of cow's milk-based infant formula may induce mucosal inflammation and increase gut permeability. Signs of intestinal inflammation and increased gut permeability have been observed among children with T1D [39,40]. Since the subjects were prevalent cases, the possibility that the inflammation is a consequence of diabetes cannot be ruled out. Furthermore, celiac disease, another autoimmune-mediated chronic disease, is characterized by mucosal inflammation [39]. Children with newly diagnosed T1D have increased levels of antibodies to food proteins, especially to cow's milk [41]. This could implicate either greater exposure to cow's milk, increased reactivity to cow's milk proteins or increased intestinal permeability to cow's milk proteins in newly diagnosed children with diabetes [42]. Children who subsequently progressed to T1D had elevated IgG antibody levels to β-lactoglobulin at the age of 3–18 months and elevated IgA antibody levels to cow's milk formula at the age of 9 months [43]. Bovine insulin has been hypothesized to play a crucial role in β-cell autoimmunity: young children who present with early signs of β-cell autoimmunity appear to lack the capacity to develop oral tolerance to bovine insulin and initial immunization to bovine insulin may later divert into a response targeting human insulin and insulin-producing β-cells [44].

Subjects with T1D may have a proliferative T cell response to wheat polypeptides with a proinflammatory cytokine profile [45]. Whether these findings may reflect intestinal inflammation, defective oral tolerance and/or increased gut permeability remains to be shown.

If the observed association of early age at introduction of root vegetables with advanced β-cell autoimmunity reflects a true relationship, the question arises whether natural or other toxins could be involved in the pathogenesis of T1D as suggested by studies in rodents [46] and fetal porcine islet cell culture [47]. In addition, ingredients such as starch that are added to the baby foods during industrial processing or food preparation at home could play a role, although there is no evidence for this.

Table 2. Prospective studies evaluating the associations between age at introduction of complementary feeding and Type 1 diabetes.

Exposure and age at exposure	Early pre-T1D	Advanced pre-T1D	Ref.
Randomized trials			
Cow's milk-based vs extensively hydrolyzed formula during the first 6–8 months	↑		[8,52]
Prospective cohort studies			
Cow's milk at <2–3 months vs later	↑		[31]
Gluten-containing cereals at <3 months vs later	↑		[30]
Cereals at <4 and >6 months vs 4–6 months	↑		[13]
Fruits at ≤4 months vs later		↑	[32]
Roots and potato <3 months vs later		↑	[14,32]

Cow's milk was also studied in [13,14,30,32], but no association was observed. Cereals were also studied in [14,32], but no independent association was observed.
↑: Increased risk; Pre-T1D: Preclinical Type 1 diabetes.

The early introduction of complementary foods may result in higher energy intake, which could cause β-cell stress and thereby induce β-cell autoimmunity.

It is possible that an extensively hydrolyzed infant formula could protect from β-cell autoimmunity by postponing exposure to intact cow's milk proteins. It may also be that a extensively hydrolyzed formula could decrease intestinal permeability or stimulate the maturation of regulatory T cells in the gut-associated lymphoid tissue leading to suppression of signs of β-cell autoimmunity [8,33].

Findings from the TRIGR pilot intervention study [8], and the fact that pre-T1D is not known to cause any detectable symptoms, speak against reverse causation between dietary exposures and T1D.

Conclusion & future perspective

Although inconclusive, the current evidence suggests that very early age at introduction of complementary foods (before 4 months of age) may be important in the development of T1D. Early introduction of cow's milk is a suspected risk factor. Case–control studies support this view, but are more prone to bias than prospective cohort studies. For example, selection bias or recall bias may have affected the results. These sources of potential bias are avoided in prospective cohort studies. As the introduction of cow's milk has not been associated with the risk of T1D in the

majority of cohort studies published so far, the evidence as a whole is still inconclusive and more research is needed.

Early introduction of solid foods is a risk factor for T1D according to findings of birth cohort studies. The foods identified as risk factors are cereals and root vegetables, which are also the typical first solids introduced to the infant. So far, only a few results have been published on this issue, and the response variable used has been early or advanced pre-T1D not clinical disease. More research is needed before firm conclusions can be drawn.

The ongoing large prospective cohort studies such as DIPP [48], DAISY [13] and the international TEDDY study [49], as well as the first nutritional primary prevention study in T1D, the TRIGR study [33], will generate new insights into the significance of early feeding in the pathogenesis of T1D. In contrast to the findings in autoimmune diseases, in which early introduction of foods seems to have adverse effects, early introduction of complementary feeding seems to protect from another group of immune-mediated diseases, namely asthma, allergic rhinitis and atopic sensitization [50,51]. The evidence for the health effects of infant feeding needs to be considered as a whole when updating recommendations.

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