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ORIGINAL CONTRIBUTION

Early infant feeding and type 1 diabetes

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Abstract
Background Infant feeding practices, particularly the type of milk feeding, have been associated with the development of type 1 diabetes.
Aim of the study We studied the relationship between early infant feeding (during the first year of life) and diabetes in a large population-based cohort.
Methods In 1994–1995, 6,209 healthy full-term newborns participated in a study examining the effect of supplementary feeding, on development of allergy to cow's milk, in maternity hospitals. All supplements in the maternity hospitals were known. Mothers recorded the feeding of infants prospectively at home. In August 2006, from a nationwide diabetes registry, 45 children from our cohort were listed as having type 1 diabetes.
Results The distribution of cases was similar in the randomized feeding groups: 9/1,789 in the group that received adapted cow's milk-based formula; 12/1,737 in those who received extensively hydrolyzed formula; 16/1,859 in those who received banked human milk; and 8 among those 824 exclusively breast-fed in the hospital. When children who had received cow's milk-based formula in the maternity hospital were compared with those without such exposure, less number of children in the former group had diabetes by age 8 ($P = 0.026$), but by the end of the follow-up (11.5 years) the difference disappeared ($P = 0.16$). Length of breast-feeding and introduction of cereals and other solid foods were similar among those developing type 1 diabetes and those remaining healthy, while early regular daily feeding with cow's milk-based formula tended to associate with lower risk for type 1 diabetes (OR 0.66; 95% confidence interval 0.38–1.13; $P = 0.08$).
Conclusions In an extended, secondary analysis of a population-based cohort, very early exposure to cow's milk is not a risk factor for type 1 diabetes; it may in fact diminish its appearance before age 8.

Keywords Type 1 diabetes · Infant feeding · Breast milk · Infant formula

Abbreviation
CM Cow's milk

Introduction

Type 1 diabetes results from a loss of insulin-producing beta-cells in the pancreas. Heredity markedly affects the morbidity. The major genes associated with type 1 diabetes are those determining antigen presenting HLA-class II structures [4]. Environmental factors, also, play a major role in the development of type 1 diabetes. For identical twins, the concordance of diabetes is only 40% and in HLA identical siblings 20% [10]. Further, genetic qualities change in the population very slowly, while we have seen a very rapid and large increase in the prevalence of type 1 diabetes in several developed countries. In Finland, for instance, its prevalence has increased twofold in the last 25 years [6]. Environmental events initiating, maintaining and accelerating the apoptotic death of insulin-producing beta-cells in the pancreas remain unknown [14].

A similar change as for type 1 diabetes has been seen in the prevalence of diseases with another immune reaction, allergic diseases [2]. Environmental factors that affect the

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development of immune regulation have been speculated to be responsible for both changes. Gut-associated lymphoid tissues are the largest immune structure in humans. The main stimulant of this structure is the indigenous bacterial flora. Stimulation is needed for the development of regulatory T cells in experimental animals [19]. In addition, the amount and timing of the introduction of food antigens directly affect the development of the gut-associated immune organ by either influencing tolerance or immunity [16]. Much attention, therefore, has been paid to the impact of early infant feeding on the development of type 1 diabetes. All early studies focusing on the matter have been retrospective [5], and most recent prospective studies have been performed on infants at high risk of developing type 1 diabetes [9, 12, 17, 18, 26–28]. The effect of early feeding on the development of such immune-mediated diseases, such as type 1 diabetes and allergy, may interact with heredity, and the effect of early exposure to foreign food antigens may be different among those with a high risk of developing the disease and those without this risk [8]. We, in studying the effect of early exposure to cow's milk (CM) formula on the development of CM allergy [20], have an exact knowledge of the supplements given to a large number of newborn infants at maternity hospitals and in a large proportion of these infants also during the first few months of life. From a nationwide registry, we sought individuals who had contracted type 1 diabetes by the age of 11–12 years; 45 individuals from 6,209 names recorded were identified. In this unselected group, we studied the association between early feeding events with the development of type 1 diabetes.

Subjects and methods

Subjects

For the present study, we used a cohort of children recruited for the study on the importance of supplementary feeding at maternity hospitals for the development of CM allergy [20]. Between August 1994 and November 1995, a total of 15,400 healthy full-term infants were born in the metropolitan region of Helsinki. The mothers of these infants were invited to participate in the study. A total of 6,267 agreed to participate; 58 were lost for various reasons, leaving 6,209 participants. All mothers were encouraged to breast-feed their infants, but only 824 infants received only their mother's breast milk. In the remaining 5,377, supplementary milk was given at the maternity hospital. Indications to give supplementary milk were: insufficient quantity of breast milk, danger of hypoglycemia, excessive weight loss (more than 8%) or development of hyperbilirubinemia. These babies were randomized to receive one of three supplements: an adapted CM formula Tutteli® (Valio Ltd, Finland; $n = 1{,}789$), extensively hydrolyzed whey-based formula (Pepti-Junior®, Nutricia, The Netherlands; $n = 1{,}737$) or banked, pooled pasteurized human milk ($n = 1{,}859$). The CM formula was a ultra high temperature treated liquid formula, with a protein concentration of 15 g/L, and its whey:casein ratio was 60/40. Also at home, mothers were encouraged to exclusively breast-feed their babies, but if needed, to give regular adapted CM formula as a supplement. Mothers were asked to record daily the amount and type of infant formula given daily during the first 8 weeks. A total of 4,661 (75%) returned the records. We inquired after the frequency and type of liquid and solid feeds of infants at the ages of 6 and 12 months for the preceding 6 months; the response rates to these were 77 and 74%, respectively.

Children who contract type 1 diabetes are eligible for free care of the disease when registered at the National Health Institute. Therefore, this institute has a complete knowledge of all children with type 1 diabetes. In August 2006, when the oldest children in the study were 12 years old, patients with type 1 diabetes, among the 6,209 study persons, were sought from the institute's database and 45 patients were found. We did an extended secondary analysis of the existing data on the feeding of the infants, comparing those who contracted type 1 diabetes with those who remained healthy. The ethics committee of the National Health Institute approved the study plan.

Methods

The distribution of cases with type 1 diabetes, according to various feeding regimens, was tested by Pearson χ^2 test. The amounts of CM-based formula consumed by infants who contracted type 1 diabetes as well as those who remained diabetes-free were compared by t test. The duration of breast-feeding and the ages of introduction of various foods were also compared by t test. Ages at the first feed with cow's milk-based formula, introduction of vegetable solids, cereals and dairy milk, as well as the age when daily feeding with cow's milk-based formula was started and that of total breast-feeding were categorized dichotomous at the medians. Odds ratios for groups with early and late change for the above events in feeding were calculated. Logistic regression analysis was performed to evaluate the risk related to the development of type 1 diabetes and the feeding variables. Kaplan–Meier survival analysis was used for the comparison of the appearance of type 1 diabetes in the maternity hospital supplementary group exposed to cow's milk formula with those not exposed. SPSS version 15 was used for the analysis.

Table 1 Supplementary feeding in the maternity hospital and development of type 1 diabetes

	Adapted CM- based formula		Hydrolyzed whey-based formula		Banked, pasteurized breast milk		Own mothers′ breast milk	
	n (%)	%	*n* (%)	%	*n* (%)	%	*n* (%)	%
Developed type 1 diabetes ($n = 45$)	9	20[a]	12	27[a]	16	36[a]	8	18[a]
	0.50[b]		0.69[b]		0.86[b]		0.97[b]	
No diabetes ($n = 6164$)	1,780	29[c]	1,725	28[c]	1,843	30[c]	816	13[c]

Pearson $\chi^2 = 0.49$ (among the distribution of type 1 diabetes in various feeding groups)

[a] Percentage of all children who contracted type 1 diabetes

[b] Percentage of children of the whole feeding group, who contracted type 1 diabetes

[c] Percentage of all children who did not contract type 1 diabetes

Results

Development of type 1 diabetes in the cohort

By the mean age of 11.5 years, 45 children were reported to the registry as having type 1 diabetes. We had followed the cohort altogether for 71,300 years, giving an incidence of 63/100,000 years.

Supplementary milk feeding in maternity hospitals

We found no association in the number of cases that developed type 1 diabetes between the study groups receiving a randomized supplement and those fed on mothers' own breast milk at the maternity hospital (Table 1). When children who had received regular CM formula at the maternity hospital were compared with those without exposure to the CM formula, the cumulative number of children developing type 1 diabetes until the age of 8 years was significantly lower among those given CM (Fig. 1, $P = 0.026$). However, by the end of the follow-up, no difference in the prevalence of type 1 diabetes was seen between those who had CM formula and those who did not have CM in the maternity hospital (Fig. 1; $P = 0.16$). Those who had only breast milk, either randomized to receive banked human milk or exclusively breast-fed by their own mothers, developed type 1 diabetes in the same proportion as those supplemented with extensively hydrolyzed whey-based formula or regular adapted CM-based formula (data not shown).

Seven of the nine infants who developed type 1 diabetes in the randomized CM formula group received CM formula already during the 1st day of life. The amount of CM formula during the 1st day of life was similar as in those developing or not developing the disease (mean 57 vs. 53 ml; $P = 0.8$). During the entire time spent in the maternity hospital, the amounts were similar: among those nine infants who developed type 1 diabetes, the mean amount being 209 ml and in the remaining 1,780 newborns, 289 ml ($P = 0.24$).

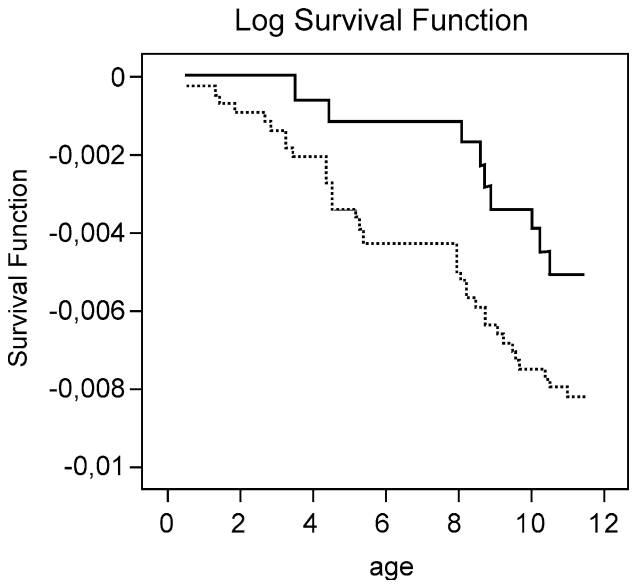

Fig. 1 Cumulative appearance of type 1 diabetes among children who had different supplements in the maternity hospital. The proportion of children with type 1 diabetes is given in the *y* axis. *Continuous line* children received regular cow's milk-based formula, *dotted line* not given cow's milk-based formula in the maternity hospital. The cumulative appearance by the age of 8 years was significantly lower in children who had CM-based formula in the maternity hospital ($P = 0.026$)

CM formula during the first 2 weeks of life according to home recording

Of the 45 infants, 12 (27%) who developed diabetes had received CM formula during the first 2 weeks; among those remaining without type 1 diabetes, the proportion was the same, 1,682 out of 6,164 (27%). Those 12 who later developed diabetes had received a similar mean amount of CM-based formula as those 1,683 who remained healthy

(mean 1,044, SD = 1,149 ml; 1,233 ml, SD 1,472 ml, respectively).

Later changes in infant feeding and development of type 1 diabetes

The distribution of infants exposed to CM formula before the age of 2 months was similar among those who developed type 1 diabetes and those who did not. Before the age of 2 months, 67% (3,352) and 56% (18) of the respective groups had had the exposure. In 584 infants, CM formula was given only after the age of 6 months; among these 5 developed type 1 diabetes ($P = 0.48$ by χ^2 test in comparison with those who received CM earlier).

The first CM-based feeding had been given to infants developing type 1 diabetes at the same age as to those remaining healthy (Table 2). Various vegetable feeds were the next non-human feed offered to the infants; those developing type 1 diabetes tended to have had these feeds later than those remaining healthy (mean ages 4.0 and 3.7 months, respectively; $P = 0.09$). Cereals were offered at the same time to both groups. In only 43 infants, cereals, mostly oats, were given at or before the age of 3 months; introduction occurred between 3 and 6 months in 3,471 and at an age over 6 months in 1,208 infants. The proportion that contracted type 1 diabetes in these two groups was similar (9/1,208 vs. 21/3,471; $P = 0.68$).

Daily feeding with CM-based formula tended to start earlier among those who remained without type 1 diabetes than among those who contracted the disease (Table 2). Odds ratios for developing type 1 diabetes among children who had early daily feeding with cow's milk-based formula tended to be lower than among those with later start of daily feeding (Table 3). When the dichotomized variables for the first feed with CM-based formula, introduction of vegetables and of cereals, daily feeding with cow's milk-based formula and total duration of breast-feeding were used in a logistic regression model, late start of daily CM formula feeding significantly increased the odds ratio for type 1 diabetes: OR 1.2 (95% CI 1.1–8.7; $P = 0.026$). The total duration of breast-feeding was similar in the groups (Tables 2, 3). At the time of the last inquiry at the age of 12 months, 232 mothers were still breast-feeding: 2 mothers of infants who later developed type 1 diabetes (2/31; 6.5%) and 230 out of 4,635 (5.0%) of those who remained diabetes-free.

Discussion

The present study has the advantage of the exact knowledge of the early exposure to CM formula, even in small amounts in the maternity hospital. This type of exposure often takes place in infants who are then exclusively breast-fed or have a long partial breast-feeding. We infer that the early contact with cow' milk proteins delays the onset of type 1 diabetes past age 7 years. In contrast, delaying the exposure to intact CM even till the age of 6 months reduced the appearance of type 1 diabetes-specific autoimmune markers in a pilot study of 242 infants at high risk for type 1 diabetes [1]. Subjects in that cohort had a 10 times higher genetic risk than our population-based cohort.

Early epidemiological studies cited in a review [5] suggest that either early, regular introduction of CM proteins promotes the development of type 1 diabetes or longlasting breast-feeding is protective against it. This meta-analysis of epidemiological studies before 1994 revealed that a short breast-feeding resulted in an odds ratio

Table 2 Infant feeding during the first few years of life in a population-based cohort

Variable	Infants who contracted type 1 diabetes		Infants without type 1 diabetes		*P*
	n	Mean in months (SD)	*n*	Mean in months (SD)	
First feed of CM-based formula	32	2.2 (3.0)	5,002	1.7 (2.6)	0.32
Introduction of vegetable feeds	33	4.0 (0.8)	5,007	3.7 (0.8)	0.09
Introduction of cereals	30	5.3 (0.7)	4,649	5.3 (0.9)	0.92
Daily feeding of CM-based formula	28	5.3 (3.6)	4,204	4.1 (3.2)	0.08
Total duration of breast-feeding	30	6.8 (4.0)	4,416	6.1 (3.3)	0.29
Introduction of dairy milk	25	11.4 (0.8)	3,660	11.1 (1.4)	0.1

Table 3 Odds ratios for development of type 1 diabetes related to the age of introduction of various foods

Feeding variable and age (months)	Type 1 diabetes (total number)	*P* odds ratio (95% confidence interval)
First feed with CM formula:		0.61
Before 0.1	15 (2586)	0.91 (0.63-1.32)
After 0.1	17 (2448)	1.09 (0.79-1.52)
Introduction of vegetables		0.13
Before 3.9	11 (2330)	0.72 (0.44-1.17)
After 3.9	22 (2710)	1.24 (0.97-1.58)
Introduction of cereals		0.39
Before 5.01	17 (3008)	0.88 (0.64-1.21)
After 5.01	13 (1671)	1.22 (0.81-1.83)
Daily feeding with CM formula		0.08
Before 3.8	9 (2063)	0.66 (0.38-1.13)
After 3.8	19 (2169)	1.33 (1.03-1.72)
Total breast-feeding		0.78
5.8 or less	13 (2038)	0.95 (0.63-1.42)
More than 5.8	17 (2406)	1.05 (0.77-1.43)
Introduction of dairy milk		0.94
Before 11	13 (1889)	1.01 (0.70-1.48)
After 11	12 (1796)	0.99 (0.65-1.48)

1.5-fold that observed with longer breast-feeding, and early introduction of CM formula increased the risk similarly [5]. As the great majority of infant formulas in Western countries contain intact CM proteins, these factors are highly dependent on each other. Attempts to analyze them separately suggest that early introduction of CM proteins has the greatest impact [25]. Recent large prospective epidemiological studies show no difference in the exposure to CM formula or duration of breast-feeding among high-risk infants for type 1 diabetes, who either developed type 1 diabetes-specific auto-antibodies during early childhood or remained antibody-negative [17, 26, 28]. However, in a population-based study, short breast-feeding carried a higher risk for diabetes-associated auto-antibodies during the first 2.5 years of life [27].

Retrospective questionnaires most likely do not reveal such short exposures, and exposures in maternity hospitals may be unknown to mothers. According to our study, even a very early exposure to CM formula did not increase the risk of contracting type 1 diabetes during the first 12 years of life. In fact, early exposure to CM formula in maternity hospital during the first 5 days protected against the development of type 1 diabetes during the first 7 years of life. This is the age group among whom a recent study showed a more than twofold increase in the incidence of type 1 diabetes between 1980 and 2005, while among the group of 10–14 years old, the increase was less marked [6]. During the past 15 years in maternity hospitals in Finland, so-called "Baby Friendly Hospital Initiative" has been practiced with the elimination of cow's milk formulae [7]. Whether the association between this and the trend in diabetes incidence is only timely or, as our results suggest, a causal one remains speculative and a much larger study population with exact knowledge of early feeding is needed to solve the problem. Earlier start of regular, daily feeding of cow's milk-based formula was associated with lower risk of type 1 diabetes compared to the risk in infants with later start of the same feeding pattern. We infer that for the optimal development of gut-associated immune system and its regulatory functions, stimulation by food proteins is advantageous as found in an experimental study [15].

The association of the length of breast-feeding and prevalence of type 1 diabetes was suggested on the basis of the increase in the prevalence of diabetes at the same time as the length of breast-feeding decreased and a leveling of diabetes incidence when breast-feeding duration increased [3]. However, in recent decades, breast-feeding times have increased in many developed countries. In Finland, the percentage of infants breast-fed at the age of 6 months has increased from 10% in 1970 to 40% in 1995; nevertheless, the incidence of type 1 diabetes during the same period has nearly doubled [24]. In 2005, 55% of Finnish infants were breast-fed at age 6 months [7], and during the preceding decade the increase in the incidence of type 1 diabetes had accelerated [6]. We neither found any association between breast-feeding duration and the appearance of type 1 diabetes in the present study.

Gluten has been proposed to have a diabetogenic effect based on both experimental data and epidemiological studies [13]. In two large prospective studies, the time of

introduction of gluten-containing cereals was associated with the risk of developing type 1 diabetes-associated autoimmune antibodies [18, 28]. The study from Colorado indicated a higher risk for infants exposed to cereal between the age 0 and 3 months and after the age of 7 months, compared to those exposed between age 4–6 months [18]. In a German study, the same risk was observed among those exposed to gluten-containing foods before the age of 3 months [28]. Among Finnish children with HLA-conferred susceptibility to type 1 diabetes, introduction of various cereals early or late had no impact on the risk for advanced beta-cell autoimmunity [26]. In an unselected Swedish cohort, late introduction of porridge carried an increased risk for type 1 diabetes-associated antibodies, while no such risk was seen with early introduction [27]. In that study, like in ours, early introduction of cereals was a rare event; in both studies, less than 1% of infants were exposed before the age of 3 months. Moreover, in our group, the cereal most commonly offered first was oats. Storage proteins in oats may have quite different immune stimulation effects from those in wheat; e.g., celiac patients tolerate even large amounts of oats [11]. However, late introduction of cereals also had no impact on the development of type 1 diabetes in our study group.

The study on children with HLA-conferred susceptibility to type 1 diabetes showed an increased risk for developing disease-associated auto-antibodies among those receiving fruit- and berry-containing baby foods early [26]. We did not pose questions on these products separately, but vegetable supplementation was started later among those who subsequently contracted type 1 diabetes than among those who did not. This difference was not, however, significant. These findings suggest that those at high genetic risk for type 1 diabetes may react differently to environmental stimuli than those from the general population. A similar contradiction was observed between our study showing no benefit of elimination of CM proteins till the age of 6 months, but in fact advantage among those with very early contact with cow's milk in the maternity hospital and those who had it earlier on a daily basis. Among high-risk infants, careful elimination of CM resulted in a significant reduction of type 1 diabetes-associated auto-antibodies [1]. Infants in the Trial to Reduce IDDM in the genetically at-risk (TRIGR) pilot study in maternity hospitals received either study formula or extensively hydrolyzed formula, and early contact with CM-based formula was therefore carefully excluded [1]. The effect of infant feeding on the appearance of allergic disease in childhood is different among those with familial risk for allergy and those without such a risk [22]. While exposure to high endotoxin concentrations reduced the incidences of allergic diseases to a great extent, the effect of this exposure seems to depend on the genotype of the child [23]. We showed that the magnitude of immune response measured as antibodies to CM proteins depends on the child's HLA antigens [21], further stressing the importance of the interaction of genes and immune response to environmental antigens.

We observed no significant differences in the amounts or timing of early supplementary feeding in infants who later contracted type 1 diabetes compared with those in the same unselected population-based cohort. Based on those who contract type 1 diabetes, we infer that the effect of early infant feeding may be different among those at high genetic risk for disease and in a population-based group.

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References

1. Akerblom HK, Virtanen SM, Ilonen J, Savilahti E, Vaarala O, Reunanen A, Teramo K, Hämäläinen AM, Paronen J, Riikjarv MA, Ormisson A, Ludvigsson J, Dosch HM, Hakulinen T, Knip M (2005) Dietary manipulation of beta cell autoimmunity in infants at increased risk of type 1 diabetes: a pilot study. Diabetologia 48:829–837
2. Bach JF (2002) The effect of infections on susceptibility to autoimmune and allergic diseases. N Engl J Med 347:911–920
3. Borch-Johnsen K, Joner G, Nadrup-Paulsen T, Christy M, Zachau-Christiansen B, Kastrup K, Nerup J (1984) Relation between breast-feeding and incidence rates of insulin-dependent diabetes mellituls. Lancet 2:1083–1086
4. Daneman D (2006) Type 1 diabetes. Lancet 367:847–858
5. Gerstein HC (1994) Cow's milk exposure and type I diabetes mellitus. a critical overview of the clinical literature. Diabetes Care 17:13–19
6. Harjutsalo V, Sjöberg L, Tuomilehto J (2008) Time trends in the incidence of type 1 diabetes in Finnish children: a cohort study. Lancet 371:1777–1782
7. Hasunen K, Ryynänen S (2006) Infant feeding in Finland 2005. Reports of the Ministry of Social Affairs and Health, vol 19, pp 1–70
8. Hoffjan S, Nicolae D, Ostrovnaya I, Roberg K, Evans M, Mirel DB, Steiner L, Walker K, Shult P, Gangnon RE, Gern JE, Martinez FD, Lemanske RF, Ober C (2005) Gene–environment interaction effects on the development of immune responses in the 1st year of life. Am J Hum Genet 76:696–704
9. Hummel M, Fuchtenbusch M, Schenker M, Ziegler AG (2000) No major association of breast-feeding, vaccinations, and childhood viral diseases with early islet autoimmunity in the German BABYDIAB Study. Diabetes Care 23:969–974
10. Hyttinen V, Kaprio J, Kinnunen L, Koskenvuo M, Tuomilehto J (2003) Genetic liability of type 1 diabetes and the onset age among 22,650 young Finnish twin pairs: a nationwide follow-up study. Diabetes 52:1052–1055
11. Janatuinen EK, Kemppainen TA, Julkunen RJ, Kosma VM, Mäki M, Heikkinen M, Uusitupa MI (2002) No harm from five year ingestion of oats in coeliac disease. Gut 50:332–335
12. Kimpimäki T, Erkkola M, Korhonen S, Kupila A, Virtanen SM, Ilonen J, Simell O, Knip M (2001) Short-term exclusive breast-feeding predisposes young children with increased genetic risk of

type I diabetes to progressive beta-cell autoimmunity. Diabetologia 44:63–69
13. Lefebvre DE, Powell KL, Strom A, Scott FW (2006) Dietary proteins as environmental modifiers of type 1 diabetes mellitus. Annu Rev Nutr 26:175–202
14. Mathis D, Vence L, Benoist C (2001) Beta-cell death during progression to diabetes. Nature 414:792–798
15. Menezes Jda S, Mucida DS, Cara DC, Alvarez-Leite JI, Russo M, Vaz NM, de Faria AM (2003) Stimulation by food proteins plays a critical role in the maturation of the immune system. Int Immunol 15:447–455
16. Mowat AM (2003) Anatomical basis of tolerance and immunity to intestinal antigens. Nat Rev Immunol 3:331–341
17. Norris JM, Beaty B, Klingensmith G (1996) Lack of association between early exposure to cow′s milk protein and beta-cell autoimmunity. JAMA 276:609–614
18. Norris JM, Barriga K, Klingensmith G, Hoffman M, Eisenbarth GS, Erlich HA, Rewers M (2003) Timing of initial cereal exposure in infancy and risk of islet autoimmunity. JAMA 290:1713–1720
19. Rakoff-Nahoum S, Paglino J, Eslami-Varzaneh F, Edberg S, Medzhitov R (2004) Recognition of commensal microflora by toll-like receptors is required for intestinal homeostasis. Cell 118:229–241
20. Saarinen KM, Juntunen-Backman K, Järvenpää AL, Kuitunen P, Lope L, Renlund M, Siivola M, Savilahti E (1999) Supplementary feeding in maternity hospitals and the risk of cow's milk allergy: a prospective study of 6,209 infants. J Allergy Clin Immunol 104:457–461
21. Saukkonen T, Virtanen SM, Karppinen M, Reijonen H, Ilonen J, Räsänen L, Åkerblom HK, Savilahti E (1998) Significance of cow's milk protein antibodies as risk factor for childhood IDDM: interactions with dietary cow's milk intake and HLA-DQB1 genotype: Childhood Diabetes in Finland Study Group. Diabetologia 41:72–78
22. Siltanen M, Kajosaari M, Poussa T, Saarinen KM, Savilahti E (2003) A dual long-term effect of breast-feeding on atopy in relation to heredity in children at 4 years of age. Allergy 58:524–530
23. Simpson A, John SL, Jury F, Niven R, Woodcock A, Ollier WE, Custovic A (2006) Endotoxin exposure, CD14, and allergic disease: an interaction between genes and the environment. Am J Respir Crit Care Med 174:386–392
24. Tuomilehto J, Virtala E, Karvonen M, Lounamaa R, Pitkäniemi J, Reunanen A, Tuomilehto-Wolf E, Toivanen L (1995) Increase in incidence of insulin-dependent diabetes mellitus among children in Finland. Int J Epidemiol 24:984–992
25. Virtanen SM, Räsänen L, Ylönen K, Aro A, Clayton D, Langholz B, Pitkäniemi J, Savilahti E, Lounamaa R, Tuomilehto J, Åkerblom HK (1993) Early introduction of dairy products is associated with increased risk of insulin-dependent diabetes mellitus in Finnish children. Diabetes 42:1786–1790
26. Virtanen SM, Kenward MG, Erkkola M, Kautiainen S, Kronberg-Kippila C, Hakulinen T, Ahonen S, Uusitalo L, Niinisto S, Veijola R, Simell O, Ilonen J, Knip M (2006) Age at introduction of new foods and advanced beta cell autoimmunity in young children with HLA-conferred susceptibility to type 1 diabetes. Diabetologia 49:1512–1521
27. Wahlberg J, Vaarala O, Ludvigsson J (2006) Dietary risk factors for the emergence of type 1 diabetes-related autoantibodies in 21/2-year-old Swedish children. Br J Nutr 95:603–608
28. Ziegler AG, Schmid S, Huber D, Hummel M, Bonifacio E (2003) Early infant feeding and risk of developing type 1 diabetes-associated autoantibodies. JAMA 290:1721–1728