Early Introduction of Dairy Products Associated with Increased Risk of IDDM in Finnish Children

SUVI M. VIRTANEN, LEENA RÄSÄNEN, KATRIINA YLÖNEN, ANTTI ARO, DAVID CLAYTON, BRYAN LANGHOLZ, JANNE PITKÄNIEMI, ERKKI SAVILAHTI, RAISA LOUNAMAA, JAAKKO TUOMILEHTO, HANS K. ÅKERBLOM, AND THE CHILDHOOD IN DIABETES IN FINLAND STUDY GROUP

Associations between infant-feeding patterns and risk of IDDM were investigated in a nationwide Finnish case-control study of 690 IDDM children <15 yr of age. Each child was matched by date of birth and sex to a randomly selected population-based control child. Univariate analysis revealed that the risk of IDDM was increased by ~1.5 in children for whom breast-feeding was terminated at <2 mo of age, doubled in those who were exclusively breast-fed for <2 mo, and doubled in those who were introduced to dairy products at <2 mo of age. In further multivariate analyses of these factors, it was found that introduction of dairy products at an early age was the most important risk factor, and the observed univariate effects of duration of breast-feeding variables were explained by their correlation with this factor. This is the first observational study to show that early introduction of dairy products is independently associated with an increased risk of IDDM. Adjustment for mother's education and age, child's birth order, or birth weight did not affect the results. *Diabetes* 42:1786–90, 1993

Animal studies, ecological correlation analyses, and immunological studies in newly diagnosed diabetic children suggest that cow's milk may increase risk of IDDM (1–4). Long duration of breast-feeding has been associated with a decreased risk of IDDM in several ecological and case-control studies (5,6), but has not been confirmed by all the studies (7). An increasing incidence of IDDM has been seen over the last few decades, despite a trend toward an increase in the duration of breast-feeding in many western countries, including Finland (8). Our studies were the first to show that, in addition to overall duration of breast-feeding, duration of exclusive breast-feeding and the age at which dairy products were introduced to the infants' diet were inversely associated with risk of IDDM (8,9). Now, a larger study population enables us to evaluate the independent effects of these various infant-feeding variables on risk of IDDM.

RESEARCH DESIGN AND METHODS

All IDDM children ≤14 yr of age who had been diagnosed in Finland from September 1986 to April 1989 were invited to participate in a nationwide Childhood Diabetes in Finland Study (10). Of 801 children invited, 94% participated in the dietary study. Birth-date–matched (the same day, a day before or after) and sex-matched nondiabetic control children were randomly selected from the Finnish national population registry. Of the control children first selected, 62% participated. After three attempts at matching, 85% of the IDDM children had control children. The control children were studied in two stages. In the first control series, data were collected from control children for cases <7 yr of age who were diagnosed from May 1988 to April 1989 (9). In the second control series, data were collected from control children 7 to 14 yr of age (8) and for younger children for whom control data were not obtained in the first control series (S.M.V., unpublished observations). Altogether, 690 case-control pairs were formed and were included in this study.

Dietary, socioeconomic, and neonatal data were collected using structured questionnaires (8). Data on infant feeding included questions on overall and exclusive duration of breast-feeding; age at which supplementary

From the Division of Nutrition, Department of Applied Chemistry and Microbiology and the Children's Hospital, First and Second Departments of Pediatrics, University of Helsinki; the Departments of Nutrition and Epidemiology and Health Promotion, National Public Health Institute, Helsinki, Finland; the MRC Biostatistics Unit, Cambridge, United Kingdom; and the School of Medicine, University of Southern California, Los Angeles, California.

Address correspondence and reprint requests to Dr. S.M. Virtanen, Division of Nutrition, Department of Applied Chemistry and Microbiology, University of Helsinki, P.O. Box 27, SF-00014, University of Helsinki, Finland.

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IDDM insulin-dependent diabetes mellitus; OR, odds ratio; CI, confidence interval; df, degree of freedom; HLA, human leukocyte antigen; IgA, immunoglobulin A; IgG, immunoglobulin G; BSA, bovine serum albumin.

TABLE 1
Correlations between infant-feeding variables and sociodemographic and neonatal characteristics in 690 IDDM and 690 control children

	Duration of exclusive breast-feeding		Duration of overall breast-feeding		Age at introduction of dairy products	
	r	*P*	*r*	*P*	*r*	*P*
Birth year of the child						
IDDM children	0.35	<0.001	0.33	<0.001	0.35	<0.001
Control children	0.34	<0.001	0.35	<0.001	0.32	<0.001
Birth weight						
IDDM children	0.09	NS	0.06	NS	0.06	NS
Control children	0.14	<0.01	0.13	<0.01	0.10	<0.05
Length of mother's education						
IDDM children	0.11	<0.05	0.09	<0.05	0.11	<0.05
Control children	0.17	<0.001	0.13	<0.001	0.13	<0.01
Length of father's education						
IDDM children	0.11	<0.05	0.06	NS	0.12	<0.01
Control children	0.12	<0.01	0.12	<0.01	0.13	<0.01
Mother's age						
IDDM children	−0.03	NS	0.10	<0.05	−0.02	NS
Control children	0.10	<0.05	0.22	<0.001	0.12	<0.01
Father's age						
IDDM children	0.06	NS	0.10	<0.05	0.03	NS
Control children	0.12	<0.01	0.19	<0.001	0.10	<0.05

milk feeding, i.e., dairy products (infant formulas, cow's milk, yogurt, and other cow's milk products), and solid foods were first introduced to the diet; and the type of supplementary milk provided. The sociodemographic variables used in this study were parents' education, age at the child's birth, and place of residence (rural versus urban; rural included countryside, municipal centers and villages, whereas urban included cities and suburbs). The neonatal variables were birth order, birth weight, possible prematurity of the child, and admission to intensive care or nursery. The only differences in sociodemographic variables between the IDDM and control children were the smaller proportion of IDDM (27%) versus control (33%) children's mothers with >13 yr of education ($P = 0.02$), and the greater proportion of IDDM (22%) versus control (18%) children's fathers <26 yr of age at the time of birth ($P = 0.03$). Of control and IDDM children, 2% and 1%, respectively, had a birth order >5 ($P = 0.04$). All other neonatal characteristics were similar among IDDM children and control children.

The study protocol was approved by the ethical committees of all participating hospitals. Comparisons between IDDM and control children were made with paired tests. The McNemar test was used for comparing frequencies between IDDM and control children. The median values of the variables that were not normally distributed were compared with the sign test, whereas the paired Student's *t* test was used for the normally distributed variables. Pearson's coefficients of correlation were calculated between infant-feeding variables and sociodemographic and neonatal variables. ORs with 95% CIs were used to estimate the effect of feeding habits on the risk of IDDM. Adjustment for confounding variables was performed by conditional matched logistic regression (11).

RESULTS

Duration of overall breast-feeding of IDDM and control children did not differ (median 5 vs. 6 mo, mean 6.6 mo for both groups). IDDM children had been breast-fed exclusively for a shorter period than were the control children (median 3 mo for both groups, mean 2.7 vs. 3.0 mo, $P = 0.006$) and had started receiving dairy products earlier (median age 3 vs. 4 mo, mean 4.3 vs. 4.7 mo, $P = 0.004$). No difference was detectable in the ages at which solid foods were introduced to IDDM and control children (median 3 mo for both groups, mean 3.5 vs. 3.6 mo).

Correlations between the infant-feeding variables and some sociodemographic and neonatal characteristics are presented in Table 1. Premature IDDM children, compared with full-term IDDM children, had been exclusively breast-fed for a shorter period of time (median 2 vs. 3 mo, $P = 0.04$) and had been introduced to dairy products earlier (median 3 mo for both groups, $P = 0.02$). IDDM children admitted to postnatal intensive care or nursery, compared with other IDDM children, received dairy products earlier (median 3 mo for both groups, $P = 0.03$). Control children living in rural areas had been breast-fed overall (median 6 mo for both groups, $P = 0.04$) and exclusively (median 3 mo for both groups, $P = 0.03$) for a longer time and had started receiving dairy products (median 5 vs. 4 mo, $P = 0.02$) later than the control children living in urban areas. The intercorrelations between the three infant-feeding variables ranged from 0.63 to 0.76 ($P < 0.001$) for IDDM and control children.

The risk of IDDM was smaller for children who were breast-fed overall for ≥4 mo compared with those who were breast-fed for <2 mo or not at all (Table 2, model 1). Children breast-fed exclusively for ≥2 mo had a smaller risk of IDDM compared with those who were breast-fed

TABLE 2
Multiple logistic regression models for risk of IDDM by overall duration of breast-feeding, age at introduction of dairy products, and duration of exclusive breast-feeding

	Unadjusted ORs (95% CI)			Adjusted ORs (95% CI)	
	Model 1 (*n* = 1208)	Model 2 (*n* = 846)	Model 3 (*n* = 1132)	Model 4 (*n* = 1016)	Model 5 (*n* = 734)
Overall duration of breast-feeding (mo)					
2–3	0.74 (0.49–1.12)			1.02 (0.59–1.76)	
4–5	**0.60** (0.38–0.95)			1.10 (0.59–2.02)	
≥6	**0.59** (0.39–0.88)			0.87 (0.47–1.63)	
Duration of exclusive breast-feeding (mo)					
2–3		**0.60** (0.42–0.85)			1.05 (0.49–2.25)
4–5		**0.43** (0.27–0.67)			0.76 (0.31–1.85)
≥6		0.60 (0.34–1.07)			1.24 (0.46–3.36)
Age at introduction of dairy products (mo)					
2–3			**0.63** (0.45–0.89)	**0.53** (0.34–0.84)	0.56 (0.25–1.27)
4–5			**0.49** (0.32–0.73)	**0.45** (0.26–0.79)	**0.38** (0.15–0.96)
≥6			**0.58** (0.40–0.82)	0.62 (0.35–1.08)	0.51 (0.21–1.27)
Log likelihood	414.8	285.8	384.9	343.0	244.4

ORs in lightface differ significantly ($P < 0.05$) from those printed in bold. Model 4 includes both overall duration of breast-feeding and age at introduction of dairy products; Model 5 includes both exclusive duration of breast-feeding and age at introduction of dairy products.

exclusively for <2 mo or not at all (Table 2, model 2). In addition, the introduction of dairy products at ≥2 mo of age was associated with a smaller risk of IDDM compared with the risk of those children receiving dairy products earlier (Table 2, model 3). Adjustment for mother's education, mother's age, child's birth order, or birth weight changed none of these results. Likewise, the adjustment for prematurity, admission to intensive care or nursery after birth, or place of residence did not affect the results.

The independent effects of overall breast-feeding and age at introduction of dairy products were studied by simultaneously introducing both factors as three dichotomous variables (2–3 mo/other, 4–5 mo/other, ≥6 mo/other) to the logistic regression model (Table 2, model 4). When duration of overall breast-feeding was also introduced to the model, only the age at introduction of dairy products remained significant. Adjustment for mother's education, mother's age, child's birth order, and birth weight changed none of the results. When both duration of exclusive breast-feeding and age at introduction of dairy products were introduced to the logistic regression model, only the age at introduction of dairy products was significant (Table 2, model 5).

Today, in Finland, mothers breast-feed their children and put off the introduction of supplementary milk feeding for a longer period of time than in the early 1970s. Therefore, we investigated whether the association between early introduction of dairy products and the risk of IDDM varied over a calendar period. ORs for age at introduction of dairy products at ≥2 mo vs. <2 mo were not significantly different, with 0.64 and 0.46 for year of birth 1972–1979 and 1980–1988, respectively, (χ^2 = 1.1, df = 1). This means that the association between age at introduction of dairy products and risk of IDDM did not differ by birth-year cohort.

DISCUSSION

In the largest population studied thus far, we showed that introduction of dairy products during early infancy, but not duration of breast-feeding, was associated with an increased risk of IDDM. This association was not affected by mother's education, mother's age, child's birth order, or child's birth weight.

Several studies have shown an inverse association between the age at which dairy products are introduced in infancy and risk of IDDM (8,9,12,13,14). Kostraba et al. (12) found that the age at introduction of any breast-milk substitute, not specifically cow's milk supplement, was associated with an increased risk of IDDM in blacks but not in whites in Pennsylvania. When they adjusted for breast-feeding status, this association became nonsignificant. However, their study had a small number of subjects and was overmatched because siblings not matched by family were used as control subjects. Recently, Kostraba et al. (13) reported from the Colorado IDDM Registry that an association between introduction of cow's milk at an early age and an increased risk of IDDM was significant only in individuals who were defined as high risk by using an HLA-DQB1 marker in a subgroup analyses. Measurement of dietary variables, their definition, and use in data analyses were not sufficiently described in their study to permit proper comparisons with our study. None of the aforementioned studies (8,9,12,13,14) adjusted for duration of breast-feeding. Because of a high intercorrelation between age at introduction of dairy products and duration of breast-feeding, it is not possible to conclude whether one variable is more important than the other without adjusting for the effect of each. Our study was the first to show that after adjustment for duration of breast-feeding, increased risk of IDDM in conjunction with early introduction of dairy products was still present.

Several types of studies have suggested a causative role for cow's milk protein in the etiology of IDDM. In diabetes-prone BB rats, cow's milk protein increased the incidence of IDDM, especially when given during the weaning period (15). In several countries, a high positive correlation was found between the per capita consumption of dairy products and risk of IDDM (2). Increased levels of IgA antibodies to cow's milk and of IgA and IgG antibodies to β-lactoglobulin were found in newly diagnosed diabetic compared with nondiabetic children (3). This finding was later confirmed in our large, nationwide Childhood Diabetes in Finland Study. Patients <3 yr of age had markedly higher IgG and IgA antibody levels to cow's milk compared with the control children. Likewise, IgG antibodies to β-lactoglobulin also were higher (16). Of these antibodies to cow's milk, the IgA antibodies to β-lactoglobulin in particular were shown to be associated with risk of IDDM (14). Recently, Karjalainen et al. (4) found that antibodies to BSA, especially to its small peptide sequence called ABBOS, distinguish newly diagnosed diabetic children from control children more clearly than does any other cow's milk antibody studied previously. It has been shown in humans that food antigens pass more easily through the neonatal than through the adult intestine (17); however, more data are clearly needed concerning the immunization and tolerance development processes in young infants.

In this study, infant-feeding data were collected from newly diagnosed diabetic children. The data collection was similar among IDDM and control children. The duration of breast-feeding in control children in this study was in agreement with the results of other Finnish studies (18). The participants did not know about the potential relationship between infant-feeding practices and risk of IDDM. Good agreement has been found between prospectively and retrospectively collected breast-feeding data, the variability being greater for retrospective data (19,20). The use of retrospective infant-feeding data in this study could have resulted in a conservative rather than an invalid conclusion (20).

In conclusion, this study is the first to show, by means of an observational study design, that the age at introduction of dairy products is associated with risk of IDDM, independently of duration of breast-feeding. This finding should be confirmed in other populations as well. An intervention study is needed to determine the possible role of cow's milk in the development of IDDM in humans.

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APPENDIX: THE CHILDHOOD DIABETES IN FINLAND STUDY GROUP

Principal Investigators: H.K. Åkerblom, J. Tuomilehto; Coordinators: R. Lounamaa, L. Toivanen, E.A. Kaprio; Data Management: J.Pitkäniemi, E. Virtala; Local Investigators: A. Fagerlund, M.v. Flittner, B. Gustafsson, C. Häggqvist, A. Hakulinen, L. Herva, P. Hiltunen, T. Huhtamäki, N-P. Huttunen, T. Huupponen, M. Hyttinen, T. Joki, R. Jokisalo, M-L. Käär, S. Kallio, E.A. Kaprio, U. Kaski, M. Knip, L. Laine, J. Lappalainen, J. Mäenpää, A-L. Mäkelä, K. Niemi, A. Niiranen, P. Ojajärvi, T. Otonkoski, K. Pihlajamäki, S. Pöntynen, J. Rajantie, J. Sankala, J. Schumacher, M. Sillanpää, M-R. Ståhlberg, C-H. Stråhlmann, T. Uotila, M. Väre, and P. Varimo.

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