Cow's Milk Exposure and Type I Diabetes Mellitus

A critical overview of the clinical literature

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OBJECTIVE — To critically review and summarize the clinical evidence relating a short duration of breast-feeding or early cow's milk exposure to insulin-dependent (type I) diabetes.

RESEARCH DESIGN AND METHODS — All relevant citations retrieved through comprehensive searching of the medical literature were critically reviewed and analyzed. Those case-control studies that minimized the possibility of bias were meta-analyzed to determine overall odds ratios (ORs) and 95% confidence intervals (CIs).

RESULTS — Ecological and time-series studies consistently showed a relationship between type I diabetes and either cow's milk exposure or diminished breast-feeding. In the case-control studies, patients with type I diabetes were more likely to have been breast-fed for <3 months (overall OR 1.43; 95% CI 1.15–1.77) and to have been exposed to cow's milk before 4 months (overall OR 1.63; 95% CI 1.22–2.17). Slightly lower ORs were obtained when all of the case-control studies were meta-analyzed in a sensitivity analysis.

CONCLUSIONS — Early cow's milk exposure may be an important determinant of subsequent type I diabetes and may increase the risk ~1.5 times.

Type I diabetes mellitus develops as a consequence of autoimmune destruction of the insulin-producing β-cells of the pancreatic islets (1). Although the precise cause of the autoimmune reaction is unknown, the association of human leukocyte antigen (HLA) class 2 antigens (2,3) as well as the increased risk of type I diabetes in first-degree relatives of patients with type I diabetes (3) and other autoimmune disorders (4) are consistent with a genetically acquired immune defect in susceptible individuals. Recent serological evidence that this immune defect may be triggered by exposure to a protein found in cow's milk (5) has raised many concerns regarding the safety and advisability of feeding cow's milk–based products to neonates. Although animal and laboratory evidence exists to justify these concerns (6,7), studies involving humans and clinical end points have generated conflicting results that both support and undermine the cow's milk–diabetes hypothesis. These differing results prompted this critical review of the epidemiological and clinical literature relevant to a possible link between cow's milk and type I diabetes.

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Received for publication 8 March 1993 and accepted in revised form 10 June 1993.

Type I diabetes, insulin-dependent diabetes mellitus; HLA, human leukocyte antigen; OR, odds ratio; CI, confidence interval.

RESEARCH DESIGN AND METHODS

— A comprehensive search of the medical literature was completed to identify all relevant articles dealing with neonatal feeding and type I diabetes in humans. Three Medline searches using various search strategies were done independently by one clinician and two medical librarians with expertise in searching the medical literature. Citations were also found through review of the bibliographies of all retrieved articles and through surveying experts involved in research into the etiology of type I diabetes.

Retrieved citations were classified according to their focus, which was determined from the title, abstract, or text. Articles or letters to the editor were eligible for inclusion in this review if they reported original research dealing with both type I diabetes and cow's milk exposure or avoidance and were published in peer-reviewed journals. Articles were excluded if they exclusively used surrogate markers for either type I diabetes (such as the presence of islet cell antibodies) or cow's milk exposure (such as the presence of antibodies to cow's milk).

Included articles were then classified according to study design. Case-control studies were analyzed to determine the source and nature of cases and control subjects and the method by

Table 1—*Methodological criteria applied to case-control studies*

Inclusion of ≥75% of eligible diabetic patients.
Unbiased selection of unrelated nondiabetic control subjects.
Control subjects derived from the same population as diabetic subjects.
An identical means of determination of infant feeding practices in both diabetic and nondiabetic groups.
Blind determination of early feeding history (i.e., the interviewer was not aware of the subject's diabetes status).
Identification of diabetic patients from incident cases.

which exposure to cow's milk was determined. They were then categorized as to whether or not they met methodological criteria chosen to identify studies that minimized the possibility of bias. These criteria, listed in Table 1, ensured that a representative proportion of all incident cases were included (criteria 1 and 6), that an unrelated control group was chosen in which the possibility of biased selection was minimized (criterion 2), that control subjects and cases were derived from the same population (criteria 3), and that an equally reliable history of breast-feeding or early cow's milk would be available for both cases and control subjects (criteria 4 and 5). Studies that most closely satisfied these criteria were used to generate the conclusions of this review.

Statistical results were quoted directly from the relevant studies; to facilitate comparisons among case-control studies, unadjusted odds ratios (ORs) and 95% confidence intervals (CIs) were calculated whenever they were not provided in the original reference. Adjusted ORs from groups of studies were assessed for heterogeneity using the Q statistic and χ^2 distribution (8); unadjusted ORs were used for studies that did not report adjusted values. Overall ORs and 95% CIs were calculated for statistically homogeneous studies (8).

RESULTS— Altogether, 60 citations were reviewed and classified based on their content (n = 30), title, or abstract (n = 30). Twenty-two citations reported original data pertaining to the relationship between cow's milk and diabetes; 3 of these reported animal studies or laboratory end points. Thus 19 relevant studies (9–27) reported on the association of type I diabetes in humans with breast-feeding (and therefore avoidance of cow's milk) or exposure to cow's milk; 1 of these (9) reported two different study designs.

The study designs used fell into two main categories: *1*) ecological and time-series studies (9–11) in which the prevalence of type I diabetes was compared with the rate of breast-feeding or cow's milk consumption in different populations or over a specified period of time, and 2) case-control studies (9,12–25) in which the neonatal feeding histories of patients with type I diabetes and individually matched nondiabetic control subjects were compared. Studies that used population breast-feeding registries as control data also were included here, because the low prevalence of type I diabetes in the general population ensures that population data (which would include some people with diabetes) is representative of the breast-feeding habits of nondiabetic individuals. Finally, there was a letter to the editor reporting an analysis of two cohort studies (26) and an article that described the neonatal feeding history of a series of patients with diabetes (27); there were no controlled trials of exposure to cow's milk.

Time-series and ecological studies

The only study that related changes in the incidence of type I diabetes over time to changes in breast-feeding practices was done in Norway and Sweden (9). In both these countries, an inverse relationship was observed for the years 1940–1980, with the incidence of type I diabetes increasing as the prevalence of breast-feeding for at least 2 (Sweden) or 3 (Norway) months decreased.

This observation was supported in an ecological study that examined differences in the rate of breast-feeding and the incidence of type I diabetes in 18 different countries (10). Countries with the lowest prevalence of breast-feeding at 3 months of age had the highest incidence of type I diabetes ($r = -0.53$, $P < 0.05$). This study also demonstrated a positive correlation between the incidence of type I diabetes and the daily milk protein consumption in 12 different countries ($r = 0.86$, $P < 0.01$).

The link between cow's milk consumption and type I diabetes was supported further in a study of 12 countries with well-validated registries of all patients with diabetes diagnosed from 0 to 14 years of age (11). Similar to the previous study, the incidence of type I diabetes and the populations' annual milk consumption were highly correlated ($r = 0.96$). In these two studies (10,11), the cow's milk consumption data applied to the whole population and were not determined specifically for children or infants, or for patients with or without diabetes.

Case-control studies

Tables 2 and 3 summarize the 13 relevant case-control studies that were reported in 15 papers (9,12–25); 3 reports (14–16) that concern the same study populations are grouped together. As indicated in Table 3, some of these studies demonstrated that patients with type I diabetes were more likely to have a history of neonatal cow's milk exposure or a short/negative history of breast-feeding than nondiabetic control subjects; other studies failed to demonstrate such a relationship.

When the studies were classified according to their design (Table 4), a

Table 2—*Breast-feeding and or cow's milk exposure and type I diabetes*

	Diabetes cases				Control groups			
Reference	Source	Description	*n*	Cases included (%)	Description and source	*n*	Control/ case	Determination of feeding history
12	All Finnish hospitals treating childhood diabetes	Incident cases <age 7 diagnosed May 1988–April 1989	103	85	Age-matched, randomly chosen, from population registry	103	1/case	Questionnaire, mainly completed by mothers
13	All Finnish hospitals treating childhood diabetes	Incident cases ages 7–14 diagnosed September 1986–April 1989	426	85	Age- and sex-matched, randomly chosen from population registry	426	1/case	Questionnaire, mainly completed by mothers
14–16	Swedish registry: all cases of childhood diabetes	Incident cases <age 14 diagnosed September 1985–August 1986	339	84	Age-, sex-, and county-matched from Swedish population registry	528	1–2/case	Questionnaires
17	Australian registry plus hospital records	Incident and prevalent cases ages 5–18 during study	194	99	Nondiabetic, age- and sex-matched classmates	753	3–4/case	Nurse-administered questionnaire
18	Allegheny County/Children's Hospital registry	Incident cases <age 17 diagnosed 1965–1989	156/55*	93/52*	Nondiabetic case-siblings age-, race-, and birth order–matched to unrelated case	156/55*	1/case	Questionnaire, mailed to mothers
19	Montreal registry of type I diabetes	Incident cases ≤ age 17 diagnosed September 1983–February 1986	161	100	Age- and sex-matched friends (some relatives) named by case-parents or from the emergency room of two hospitals	321	1–2/case	Questionnaire, done by telephone
9	Two Danish outpatient diabetes clinics	Prevalent cases <age 18	188/78†	83/80†	Siblings	165/65†	<1/case	Questionnaire, verified by health record
					Danish general population	6,245		Population data
20	Colorado registry and Outpatient clinic	Incident cases 268 < 18 diagnosed July 1984–October 1985	268	70/54‡	Office practices plus an unrelated study group matched by age and sex	479	1.8/case	Questionnaire or structured interview
21	Colorado registry	Prevalent cases <age 18 diagnosed 1978–88; all Hispanics plus sample of non-Hispanic whites	164	60/76§	Random sample of licensed drivers in 1987 frequency matched by sex, age, and ethnicity	145	0.88/case	Questionnaire, done by participants or parents
22	New York diabetic clinic	Prevalent cases with a mean age of 14.8 years	95	—	Nondiabetic case-friends age-, social background–, and same area–matched	95	1/case	Questionnaire, done by parents
					Nondiabetic siblings	194	2.04/case	
23	Danish registry of all males developing diabetes at <age 20	Prevalent cases born 1959–1964 with available infant-feeding records	76	64	Age-matched males derived from infant-feeding recordings	154	2/case	Infant-feeding record compiled 1959–1964 by health visitors
24	British survey of doctors and general population	Incident cases 1,009 <age 15 diagnosed in 1988	1,009	63	All children born in 1980	3,754	—	Census-data controls; Questionnaires done by parents
25	Italian diabetic center	Not stated	396	—	Background population of similar age, sex, and origin	6,702	—	Population-data controls; clinic records, cases

*Whites/blacks.
†Clinic #1/clinic #2.
‡Registry/outpatient clinic.
§Hispanic/non-Hispanic white.

Table 3—*ORs for diabetes and short duration of breast-feeding or early cow's milk exposure*

Reference	Control subjects	Exposure	Reference group	Crude OR (95% CI)	Adjusted OR (95% CI)
12	Population registry	Exclusive breast-feeding <3 months	Exclusive breast-feeding ≥3 months	3.03 (1.19–7.69)	2.78 (1.08–7.14)*
		Milk before 3 months	Milk ≥3 months	2.13 (0.96–4.76)	1.96 (0.88–4.35)†
13	Population registry	Exclusive breast-feeding <3 months	Exclusive breast-feeding ≥3 months	—	1.59 (1.08–2.33)*
		Milk before 3 months	Milk ≥3 months	—	1.52 (1.11–2.08)†
14–16	Population registry	Breast-feeding <3 months	Breast-feeding ≥3 months	1.22 (0.86–1.72)	1.06 (0.66–1.70)*
				2.15 (0.91–5.12)‡	3.81 (1.10–13.29)‡
				1.70 (1.02–2.89)§	—
		Milk before 4 months	Milk ≥4 months	—	10.84 (1.17–100.4)†
17	Classmates	Breast-feeding <1 week	Breast-feeding for ≥1 week	1.44 (1.02–2.01)	1.40 (1.00–1.95)*
18	Siblings	Whites			
		No breast-feeding	Breast-feeding	2.00 (1.11–3.33)*	—
		Milk ≤3 months	Milk >3 months	—	0.6 (0.2–1.5)†
		Blacks			
		No breast-feeding	Breast-feeding	2.00 (0.71–5.00)	—
		Milk ≤3 months	Milk >3 months	—	3.3 (0.7–16.0)
19	Friends and relatives	No breast-feeding	Some breast-feeding	1.3 (0.8–2.1)	1.3 (0.7–2.5)*
9	Siblings	Breast-feeding <3 months	Breast-feeding ≥3 months	1.68 (1.09–2.59)*	—
	Population	Breast-feeding <3 months	Breast-feeding ≥3 months	1.60 (1.08–2.38)	—
20	Office practices, unrelated study	Breast-feeding <3 months	Breast-feeding ≥3 months	—	1.47 (0.85–2.56)*
21	Licensed drivers	No breast-feeding	Some breast-feeding	1.09 0.68–1.76)*	—
		Milk before 3 months	Milk >3 months	5.9 (0.9–40.7)	4.5 (0.9–21.4)†
22	Friends	No breast-feeding	Some breast-feeding	1.00 (0.45–2.24)*	—
	Siblings	No breast-feeding	Some breast-feeding	1.01 (0.51–2.01)	—
23	Infant-feeding registry	Breast-feeding <3 months	Breast-feeding ≥3 months	0.58 (0.33–1.02)*	—
24	Population	Breast-feeding ≤12 weeks	Breast-feeding >12 weeks	1.41 (1.19–1.68)*	—
25	Population	Breast-feeding ≤3 months	Breast-feeding >3 months	0.86 (0.70–1.07)‖	—

*Included in meta-analysis of all short duration breast-feeding ORs and plotted in Fig. 1.
†Included in meta-analysis of all cow's milk exposure ORs.
‡Diabetes diagnosed before age 4 (14).
§Diabetes diagnosed before age 6 (15).
‖Letter to the editor, not statistically homogeneous with other results.

more consistent pattern emerged. None of the studies satisfied all six methodological criteria. The studies that satisfied five of six of these criteria originated in Sweden (14–16), Finland (12,13), and Australia (17). They demonstrated that the adjusted OR for type I diabetes in patients with a history of neonatal cow's milk exposure or a short duration of breast-feeding ranged from 1.06 (95% CI 0.66–1.7) to 1.40 (95% CI 1.00–1.95) for patients developing diabetes before ages 14 (14) and 18 (17), respectively; 1.59 (95% CI 1.08–2.33) for patients developing diabetes between ages 7 and 14 (13); 1.70 (95% CI 1.02–2.89) for patients developing diabetes before age 6 (15); and 2.78 (95% CI 1.08–7.14) for patients developing diabetes before age 7 (12). In a subanalysis of patients developing diabetes before age 4 (14), the OR was 3.81 (95% CI 1.10–13.29).

When results from these four studies (12,13,14,17) were meta-analyzed (Fig. 1), the overall estimate of the OR for type I diabetes in patients exposed to <3 months of breast-feeding was 1.43 (95% CI 1.15–1.77; $P = 0.3$ for homogeneity). Three of these studies also reported the OR for type I diabetes in patients exposed to cow's milk before 3 months of age (12,13,16). A meta-analysis of these three studies yielded an overall OR of 1.63 (95% CI 1.22–2.17; $P = 0.20$ for homogeneity).

When the results from all of the peer-reviewed articles (Table 5, Fig. 1) were meta-analyzed, the OR for type I diabetes in patients exposed to <3 months of breast-feeding was 1.37 (95% CI 1.22–1.53; $P = 0.11$ for homogeneity). Similarly, the overall OR for cow's

Table 4—*Application of methodological criteria to case-control studies*

Reference	Methodological criterion*					
	1	2	3	4	5	6
12	+	+	+	+	−	+
13	+	+	+	+	−	+
14–16	+	+	+	+	−	+
17	+	+	+	+	−	+
18	+	−	+	+	−	+
19	+	−	+	+	−	+
9	+	+	+	+	−	−
20	−	+	−	+	−	+
21	−	+	?†	+	−	−
22	n/a	−	+	+	−	−
23	−	+	+	+	+	−
24	−	+	+	−	−	+
25	n/a	+	−	−	+	−

*Described in Table 1.
†Control subjects are licensed drivers, cases may not be drivers.

milk exposure before 3–4 months of age in patients (12,13,16,18,21) with type I diabetes was 1.57 (95% CI 1.19–2.07; $P = 0.10$ for homogeneity).

Other studies

In a letter to the editor, an analysis of two cohorts of children born in the United Kingdom in 1958 and 1970 followed for 16 and 10 years, respectively, failed to show any association between breast-feeding for <1 month and type I diabetes (26). A second study reported that diabetic patients who had been breast-fed developed diabetes at an older age than patients who had been bottle-fed (27); the neonatal feeding history of control subjects was not reported.

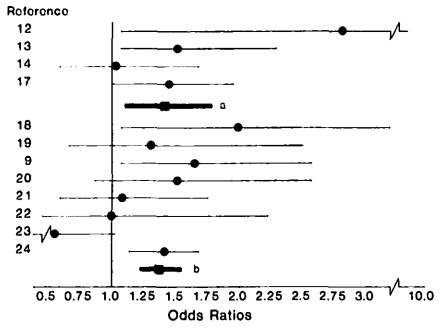

Figure 1—*The ORs and 95% CIs for <3 months of breast-feeding in type I diabetic patients for each reviewed paper. (a), The summary OR and CI for studies that minimized the potential for bias (12–14,17); (b), the summary OR and CI for all of the reviewed studies.*

CONCLUSIONS — The available time-series and ecological studies show that type I diabetes is geographically and temporally related to cow's milk consumption and neonatal feeding practices. Moreover, the ecological studies' high correlation coefficients of 0.86 ($r^2 = 0.74$) and 0.96 ($r^2 = 0.94$) suggest that 74–94% of the variation in diabetes incidence across countries may be related to differences in cow's milk consumption. These studies do not, however, prove that the relationship represents a genuine association between type I diabetes and neonatal feeding practices, because there is no way of knowing whether those people consuming the cow's milk were the same ones who developed diabetes.

The case-control study design is an efficient way to determine if a disease and an exposure are directly associated. Unfortunately, it is also particularly susceptible to bias in the selection of cases and control subjects and in the determination of exposure (28,29). Such bias may affect the validity, strength, and direction of any demonstrated association. It is minimized by studies using incident cases derived from an identifiable population, control subjects derived from the same population and ascertained similarly to cases, complete ascertainment of cases, high response rates from cases and control subjects, and objective blinded administration of well-designed questionnaires to identify exposure (29).

In this review, those case-control studies that minimized the potential for bias demonstrated an ~1.5-fold increased risk of type I diabetes with a history of early cow's milk exposure and breast-feeding for <3 months duration. The fact that this association was maintained even when the remaining studies were included in a sensitivity analysis supports the robustness and validity of this observation. This fact, and the fact that methodologically similar studies yielded both significant and nonsignificant ORs (Tables 3 and 4), also suggests that the differences in the results between individual studies likely occurred by chance. Although most of the studies did not explicitly assess cow's milk exposure, it can be assumed that most infants with a short duration of breast-feeding would have received cow's milk–based products as a dietary supplement.

Some of the reviewed studies reported ORs for varying durations of breast-feeding or ages of introduction of cow's milk. Two studies (20,25) showed a trend of increased risk of diabetes with decreased duration of breast-feeding from 12 months to 1 month of age but with nonsignificant ORs. Other studies (12,13,21) reported decreasing and nonsignificant ORs after 3–4 months of age.

Table 5—*Summary ORs for type I diabetes and neonatal feeding*

Exposure	OR (95% CI)	$P_{homogeneity}$ value
Breast-feeding <3 months		
Studies with minimal bias	1.43 (1.15–1.77)	0.30
All peer-reviewed studies	1.37 (1.22–1.53)	0.11
Cow's milk before 3–4 months		
Studies with minimal bias	1.63 (1.22–2.17)	0.20
All peer-reviewed studies	1.57 (1.19–2.07)	0.102

No consistent dose-response relationship was apparent before 3 months of age. Thus, a history of cow's milk exposure before 3–4 months of age may be more relevant for type I diabetes than the total duration of exposure.

The OR for the association of type I diabetes and early cow's milk exposure decreased with increasing age at the time of diagnosis of diabetes in the most methodologically rigorous papers (12–15,17). This is consistent with a report that diabetes developed at a later age in patients who were breast-fed compared with those who were bottle-fed (27) and suggests that a history of early cow's milk exposure may be more relevant for type I diabetes developing within the first few years of life than later on.

If early cow's milk exposure is causally related to type I diabetes, the calculated ORs will be underestimates of the magnitude of the effect for two reasons. First, only two studies (12,13) determined ORs for exclusive breast-feeding. Therefore, breast-fed subjects in the other studies may have been exposed to enough cow's milk–based formulas during their breast-feeding period to trigger type I diabetes. This contamination would obscure the relationship between diabetes and cow's milk exposure. Second, the ORs reported here were derived from studies in which control subjects were chosen from the general population. Because most of these control subjects would not be genetically susceptible to type I diabetes, they would not have developed diabetes even if they had been exposed to cow's milk (i.e., their status as control subjects would be unrelated to any early cow's milk exposure). Thus, because there would be no reason for the control subjects' early feeding history to differ markedly from that of subjects with diabetes, these studies would be biased against showing a large effect of cow's milk exposure. The fact that a positive association can be detected in spite of this bias supports the likelihood that an even stronger association would have been demonstrated if genetically susceptible control subjects were studied. Indeed, an exploratory analysis in one of the case-control studies (21) yielded a high but nonsignificant OR for early cow's milk exposure in a small number of subjects with high-risk HLA genotypes of 3.7 (95% CI 0.4–31.1).

The results of this review are consistent with the hypothesis that avoidance of cow's milk products during the first few months of life may reduce the risk of type I diabetes. The extent of this reduction may be estimated by the etiological fraction (30). For example, an OR of 1.5 suggests that up to 30% of type I diabetes cases could be prevented by removing cow's milk from the diet of 90% of the population in the first 3 months of life; this number would be even higher if the OR of 1.5 is an underestimate, as suggested above. Because the potential implications of this suggestion for neonatal feeding practices in both the general population and people at higher risk for type I diabetes are profound, definitive testing of the hypothesis is clearly warranted. A feeding intervention trial in which susceptible newborns would be randomized to receive formula with or without cow's milk and followed for the development of diabetes would most clearly resolve the issue.

Acknowledgments— The expert Medline searches done by medical librarians Ann McKibbon and Tom Flemming and the helpful comments and suggestions of Drs. R.B. Haynes and J. VanderMeulen and Professor D.W. Taylor are gratefully acknowledged.

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