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Relationship Between Cows' Milk Consumption and Incidence of IDDM in Childhood

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Objective: To compare age-standardized incidence rates of diabetes in children 0–14 yr of age and cows' milk consumption in various countries. Research Design and Methods: Ecological correlation study. Only incidence rates from diabetes registries carefully validated by the Diabetes Epidemiology Research International Study Group were used—Finland, Sweden, Norway, Great Britain, Denmark, United States, New Zealand, Netherlands, Canada, France, Israel, and Japan. Data on fluid cows' milk consumption in corresponding countries were obtained from the International Dairy Federation. Results: Correlation between milk

consumption and incidence of insulin-dependent diabetes mellitus (IDDM) was 0.96. The data fit a linear regression model, and analysis showed that 94% of the geographic variation in incidence might be explained by differences in milk consumption. Conclusions: The results support the hypothesis that cows' milk may contain a triggering factor for the development of IDDM. *Diabetes Care* 14:1081–83, 1991

Exposure to one or more environmental risk factors seems necessary to convert the HLA-linked genetic susceptibility for insulin-dependent diabetes mellitus (IDDM) into overt disease. Several possible risk factors have been studied: viruses, toxic chemicals, and certain dietary factors, but so far, no convincing evidence exists (1). Studies in BB rats and NOD mice have shown reduced incidence of diabetes associated with milk-free diets (2,3). Furthermore, increased levels of cows' milk antibodies were found in children with newly diagnosed IDDM compared with age-matched nondiabetic control children (4). During the last decade, well-standardized international incidence data for IDDM have become available. We compared the incidence of diabetes in children and cows' milk consumption in different countries in search of a possible triggering factor for diabetes.

RESEARCH DESIGN AND METHODS

Data on incidence of diabetes in children 0–14 yr of age in various countries between 1978 and 1985 were derived from the Diabetes Epidemiology Research International Study Group (5). Only registries carefully validated by this group to be virtually complete have been included. All registries have documented ascertainment >90% except Israel, where estimates of ascertainment were not available. The following registries were used: Finland, Sweden, Norway, United Kingdom, Denmark, United States (Allegheny County), New Zealand (Canterbury), Netherlands, Canada (Montreal), France, Israel, and Japan (Hokkaido). Data on fluid cows' milk consumption per person in corresponding countries were obtained from the International Dairy Federation (6). Mean consumption between 1977 and 1987 was used for analysis.

RESULTS

Figure 1 shows the association between the average annual cows' milk consumption per person and the mean annual incidence of IDDM in children 0–14 yr in age. The correlation between milk consumption and the incidence in IDDM was 0.96. The data fit a linear regression model, and analysis showed that 94% of the geographic variation in incidence might be explained by differences in milk consumption.

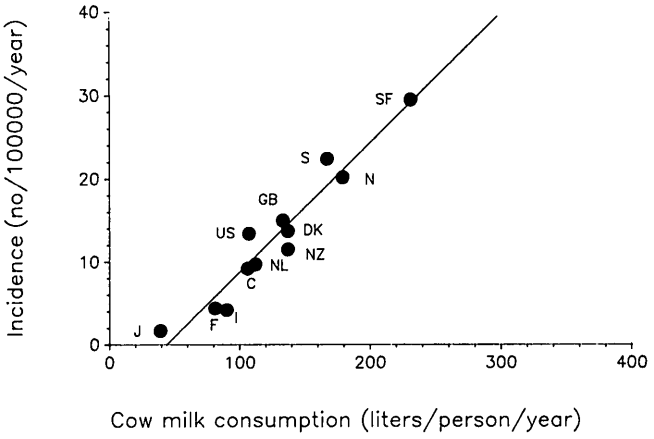

FIG. 1. Mean yearly incidence of insulin-dependent diabetes mellitus in children 0–14 yr of age by average fluid cows' milk consumption per person per yr in different countries. J, Japan; F, France; I, Israel; C, Canada; US, United States; NL, Netherlands; NZ, New Zealand; GB, Great Britain; DK, Denmark; N, Norway, S, Sweden; and SF, Finland. Incidence, $-6.77 + 0.16 \times$ consumption, $R^2 = 0.94$.

CONCLUSIONS

The results support the hypothesis that cows' milk may be a triggering factor for the development of IDDM in children. Increased levels of antibodies against cows' milk and β-lactoglobulin were found in newly diagnosed IDDM children in Finland compared with age-matched control children (4). A recent case-control study revealed a shorter duration of breast-feeding and earlier introduction of cows' milk in subsequently diabetic children (7), and a reduction of breast-feeding in Scandinavia was followed by an increased incidence of IDDM 10 yr later (8). Feeding NOD mice, which have an incidence of diabetes >70% 0–30 days of age, with a hypoallergenic infant formula (Pregestimil, Mead Johnson, Evansville, IN) containing casein hydrolysates instead of protein completely prevented diabetes up to 1 yr of age (4). Similar results were reported previously in BB rats (2).

These types of epidemiological studies are at high risk for bias when selecting countries for comparison. We used the incidence data only from registries that had been carefully validated and appeared to be complete, as judged by the Diabetes Epidemiology Research International Group (5). The milk consumption data are based on production and sales figures from well-developed and organized countries reported in a standardized manner to the International Dairy Federation. Unfortunately, no separate data of the consumption in children are available. With older data (1964–1970), Scott (9)

reported a correlation ($r = 0.86$) between consumption of unfermented milk proteins and incidence of diabetes.

Ecological studies such as this really only suggest hypotheses that need to be tested by other study designs. There is a well-established geographical IDDM incidence gradient from north to south, and in addition to differences in milk consumption, there are many other environmental and cultural factors that will distribute in the same way and therefore correlate with IDDM, i.e., a similar study of coffee consumption explained 53% of the geographic variation of IDDM incidence (10). Furthermore, in twins, only 35% are concordant for IDDM, whereas in siblings only 3–5% are concordant for IDDM, and in general, diet within families does not vary much. However, little is known about intrafamilial variability of milk consumption.

Therefore, our findings need to be interpreted with great caution. Cows' milk is an important element of childrens' food, and elimination of milk from the diet may cause more harm than benefit. However, the results may generate further research to define more precisely possible triggering factors for IDDM.

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Effect of New Oral Antidiabetic Agent CS-045 on Glucose Tolerance and Insulin Secretion in Patients with NIDDM

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Objective: To study the effects of CS-045, a newly developed thiazolidine analogue, on glucose tolerance and insulin response to oral glucose load in patients with non-insulin-dependent diabetes mellitus (NIDDM). Research Design and Methods: Nineteen NIDDM patients (mean ± SD age 48.9 ± 9.4 yr) whose previous glycemic control on diet and/or sulfonylurea (SU) therapy was judged stable but unsatisfactory (>7.8 mM) were selected for this study. CS-045 (400 mg/day p.o.) was given alone or together with the previous SU drugs for 12 wk. A 75-g oral glucose tolerance test (OGTT) was performed before and after CS-045 treatment. Results: The following results were found after CS-045 treatment. *1*) Fasting plasma glucose (FPG) and HbA_{1c} decreased ($n = 19$, FPG, 11.0 ± 2.4 vs. 8.4 ± 2.7 mM [before vs. after], $P < 0.001$; HbA_{1c}, 8.0 ± 1.1 vs. 7.4 ± 1.3%, $P < 0.005$), and glucose tolerance markedly improved. *2*) Fasting insulin (immunoreactive insulin [IRI]) and insulin response during OGTT decreased ($n = 19$, fasting IRI, 77.4 ± 49.8 vs. 56.5 ± 24.6 pM [before vs. after], $P < 0.05$; area under the curve of IRI, 540.3 ± 350.5 vs. 426.4 ± 216.3 pM · h, $P < 0.05$). Conclusions: CS-045 is effective in improving glucose tolerance without stimulation of insulin secretion in NIDDM, suggesting an effect in improving insulin sensitivity. ***Diabetes Care*** **14:1083–86, 1991**

A newly developed antidiabetic agent, (±)-5-[4-(6-hydroxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]-2,4-thiazolidinedione (CS-045), exhibited an antihyperglycemic effect in various animal models of insulin-resistant non-insulin-dependent diabetes mellitus (NIDDM) (1,2). Previous studies in animals revealed that CS-045 increases insulin