

Association Between Type I Diabetes and Haemophilus Influenzae Type B Vaccination: Birth Cohort Study

The temporal association between *Haemophilus influenzae* type b (Hib) vaccination and the development of type I diabetes in Finland was studied. The risk of type I diabetes was compared among 3 Finnish birth cohorts: those born within 24 months before the Hib vaccination trial (ie, historical controls); those vaccinated at 3 months of age and with a booster at 14 to 18 months of age; and those vaccinated only at 24 months of age. The unvaccinated cohort included 128,936 children; the 2 vaccine-eligible cohorts totaled 116,352 children. No significant differences were found at any time during the 10-year follow-up in risk of type I diabetes between the children born before the vaccination period and those vaccinated at the age of 24 months only (risk ratio 1.01; $P=0.228$). The difference in the risk between children vaccinated first at the age of 3 months and those vaccinated only at the age of 24 months also was not statistically significant (risk ratio 1.06; $P=0.545$). The authors conclude that "based both on randomized design and on the use of historical controls," it is unlikely that Hib vaccination or its timing is related to type I diabetes in Finnish children.

Karvonen M, et al. *Br Med J* 1999;318:1169-1172.

Editor's comment: *Insulin-dependent diabetes mellitus (IDDM) has been increasing in Finland over the last 3 decades. In children under 14 years of age, there has been a 2% to 5% per year increase, with a prevalence of 45/100,000 reached in 1996. This incidence is perhaps one of the highest in the world. During this*

period, children also were given an increased number of vaccines, including Hib immunizations. However, this study provides ample evidence that the concomitant expansion of Finland's childhood immunization program, at least in regard to Hib, is not responsible for the increased incidence of IDDM. The temporal association between the 2 variables does not seem to indicate that there is a cause-and-effect relationship. Unfortunately, the media, including a major segment on "ABC World News" on September 25, 1998, have reported on the alleged association between Hib vaccine and the development of this disease. I wish that the report by Dr. Karvonen and colleagues would receive equal time so that the public would not be needlessly concerned. The beneficial effects of Hib vaccination are well proven, and it would be unjustified to restrict vaccination because of potential adverse consequences that have not been proven to exist.

In addition, other studies have found no increase of type I diabetes in association with various vaccines used in childhood, including measles, BCG, and pertussis vaccines.

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Blom L, Dahlquist G. *Diabetologia* 1991;34:176-181.

Dahlquist G, Gothefors L. *Diabetologia* 1995;38:873-874.

Heijbel H, et al. *Diabetes Care* 1997;20:173-175.

Parent M-E, et al. *Diabetes Care* 1997;20:767-772.

Cow's Milk Formula Feeding Induces Primary Immunization to Insulin in Infants at Genetic Risk for Type I Diabetes

Insulin autoantibodies (IAAs) often appear as the first sign of islet cell autoimmunity in prediabetic children. Because cow's milk contains bovine insulin, the authors followed the development of insulin-binding antibodies in children fed with cow's milk formula. Bovine insulin- and human insulin-binding antibodies were analyzed by enzyme immunoassay (EIA) and IAAs were analyzed by radioimmunoassay (RIA) in 200 infants carrying *HLA-DQB1*0302* but no protective alleles. These children participated in a Finnish population-based birth cohort study. Based on the prospectively registered information, the first 100 infants (group 1) enrolled in the study who were exposed to cow's milk formula before age 12 weeks and the first 100 infants (group 2) enrolled in the study who were exclusively breast-fed for longer than the first 12 weeks of life were selected for the present study. Also studied were 11 children from the 200 infants who had developed at least two diabetes-associated autoantibodies, 98 children with newly diagnosed type I diabetes, and 92 healthy children. The authors reported that the amount of IgG antibodies binding to bovine insulin was higher at age 3 months in infants who were exposed to cow's milk formula than in infants who were exclusively breast-fed before and at 3 months of age (median, 0.521 vs 0.190; $P<0.0001$). The antibodies binding to bovine insulin cross-reacted with human insulin. None of these infants tested positive for IAAs. The levels of bovine insulin-binding antibodies declined in both groups at age 12 and 18 months; in the 11 children with at least two diabetes-associated autoanti-

bodies, the levels increased during the follow-up period ($P<0.0001$). IgG antibodies correlated with IgG2 antibodies binding to bovine insulin ($r=0.43$, $P=0.004$) and IAAs ($r=0.27$, $P=0.02$) in diabetic children, but not in healthy children.

The authors concluded that cow's milk feeding is an environmental trigger of immunity to insulin in infancy that may explain the epidemiologic link between the risk of type I diabetes and early exposure to cow's milk formulas. This immune response to insulin may later be diverted into autoaggressive immunity against beta cells in some individuals, as indicated by these findings in children with diabetes-associated autoantibodies.

Vaarala O, et al. *Diabetes* 1999;48:1389-1394.

Editor's comment: *Many studies have linked cow's milk consumed by infants to subsequent diabetes. The association is*

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based on animal experiments or indirect evidence derived from studies in which parents of diabetic children tried to recollect when their babies first started drinking milk-based formula.

The Finnish researchers who conducted this study avoided the vagaries of poor recall by studying children from birth. In so doing, they have added to the case against cow's milk. By monitoring infants in diabetes-prone families, namely, those with HLA-DQB1*0302, the scientists found that infants getting cow's milk formula were more likely to develop the immune reactions associated with insulin-dependent diabetes mellitus (IDDM) than infants fed exclusively human milk.

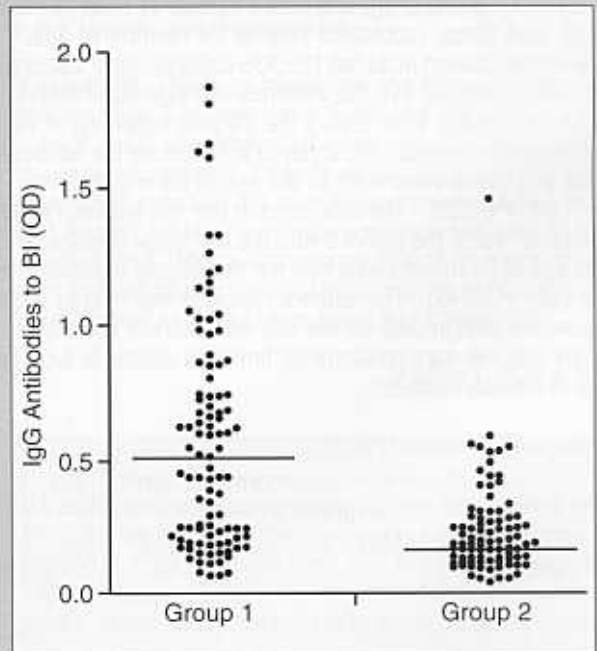
It is known that having one type of autoantibody to insulin indicates that a child has roughly a 40% chance of developing type 1 diabetes within the next decade. Additionally, having more types of these autoantibodies may be a sign of greater risk; having 3 types of autoantibodies imparts an 80% to 90% likelihood of developing type 1 diabetes. However, the precise cause of IDDM remains unclear. The children in the study were genetically predisposed to IDDM, but most will never get the disease. Something in the environment or diet, such as consuming cow's milk during infancy, may be a triggering factor.

This study presents further evidence implicating cow's milk. In Puerto Rico, fewer than 5% of mothers breast-feed their children. Instead, nearly all use formula made from cow's milk. Meanwhile, the IDDM incidence in Puerto Rico is roughly 10 times the rate seen in Cuba, where breast-feeding is nearly universal. Such findings represent circumstantial evidence suggesting that ingestion of cow's milk in the first few months of life plays a very important role in the etiopathogenesis of this disease.

To date, none of the data on cow's milk and IDDM preclude feeding cow's milk formula to infants who do not have the good fortune of being fed human milk.

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Figure
The Levels of IgG Antibodies to Bovine Insulin (BI) at Age 3 Months in Infants Who Received Cow's Milk Formula Before Age 12 Weeks (Group 1) and in Infants Who Were Exclusively Breast-Fed Until Age 12 Weeks (Group 2)



The median is marked with a line. $P < 0.0001$, group 1 versus group 2 (Mann-Whitney U test).

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A Molecular Pathway Revealing a Genetic Basis for Human Cardiac and Craniofacial Defects

The investigators have identified a gene that is deleted or mutated in patients with the DiGeorge association (DGA) of craniofacial and cardiovascular malformations. Specific defects include interruption of the aortic arch, truncus arteriosus, tetralogy of Fallot, defective immunocompetence, and hypoparathyroidism. These widespread anomalies have been attributed to a defect in the function of neural crest cells important for normal structural development. The vast majority of patients with DGA have a monoallelic microdeletion of chromosome 22q11.2. Noting that mice lacking the transcription factor *dHAND*, a factor necessary for survival of neural crest cells in the branchial arches, aortic arch, and right ventricle, have many of the anomalies present in DGA, these workers examined the genes that this protein regulates. They found it to regulate the human homologue of *Ufd1*, a gene that encodes a protease that degrades proteins linked with ubiquitin that is localized to the critical region of 22q11 associated with DGA. The investigators demonstrated that in mice, *Ufd1* was expressed in those tissues that are adversely

affected in patients with DGA. In all 182 patients with DGA and deletion of 22q11, *UFD1L* was absent. In 1 patient with DGA but no apparent chromosomal anomaly, the investigators demonstrated monoallelic deletion of exons 1 through 3 of *UFD1L* with retention of exons 4 through 12 of this gene. In the same patient, there was partial deletion of an adjoining gene, *CDC45*, a cell cycle protein. However, this gene is widely expressed. Therefore, the authors suggest that monoallelic inactivation of *UFD1L*, either by gross deletion or more subtle mutation, may be responsible for DGA. They hypothesize that the failure to degrade an as yet unidentified, ubiquitinated protein adversely affects the development of those neural crest cells necessary for normal formation of craniofacial bones, heart, thymus, and parathyroid glands.

Yamagishi H, et al. *Science* 1999;283:1158-1161.

Editor's comment: Although it remains possible and perhaps even probable that DGA and associated disorders found in