

AMERICAN ACADEMY OF PEDIATRICS

Infant Feeding Practices and Their Possible Relationship to the Etiology of Diabetes Mellitus

Work Group on Cow's Milk Protein and Diabetes Mellitus

ABBREVIATIONS. IDDM, insulin-dependent diabetes mellitus; BB, biobreeding.

Insulin-dependent diabetes mellitus (IDDM) is a common serious genetic disorder affecting a large number of children and adolescents around the world. The annual incidence rate in the United States is approximately 15 per 100 000 persons under 19 years of age, with a prevalence of 2.6 per 1000 persons. Accurate statistics on the ultimate development of IDDM in adults are limited but suggest that the annual rate varies by geographic regions. An adolescent peak occurs in most populations, but approximately equal numbers of individuals develop IDDM before and after 19 years of age.¹⁻¹⁰

The etiology of β cell damage and destruction appears to involve an interphase between genetic predisposition and environmental insult; IDDM is not inherited. Genetic alterations involving specific HLA antigens located on chromosome 6 (and other possible non-chromosome 6 alterations) result in an increased risk that β cell damage will occur. It appears, however, that less than 5% of individuals possessing the currently identifiable "diabetic genes" will ever become overtly diabetic.¹¹⁻¹⁵ The pathologic process that leads to β cell destruction is autoimmune, involving both T-cell and B-cell responses with cytokine release and free radical accumulation. Nitric oxide seems the likely candidate as the final toxic mediator.¹⁶⁻¹⁹

BACKGROUND

There is a long history of attempts to link the expression of diabetes to a variety of environmental events. The assumed relationship between mumps infection and later development of IDDM spans almost a century.²⁰ The critical unresolved questions include: 1) What triggers the autoimmune process? 2) Is there a single trigger or do many environmental insults accumulate to finally destroy the β cell mass? 3) Is there a period of special susceptibility and is this correlated with specific environmental agents? 4) What is the duration of the biologic latency period

between the triggering insult and the clinical expression of diabetes?

The available evidence supports the contention that several environmental factors may be critically involved in the initiation and continuation of the destructive autoimmune process—viral infections, several specific toxins, nutritional alterations, and emotional stress.²¹⁻²⁴ Furthermore, while single episodes (such as a mumps infection) may rarely lead to diabetes, in most cases multiple and varied insults over time are probably necessary. A recent article has discussed the possible relationship between early exposure to cow's milk protein and the development of IDDM.²⁵ Although the report provides a conceptual framework, new methodology, and impressive statistics, it is only one of a number of studies over the past 10 years that have attempted to unravel the complexities of infant feeding practices and later development of IDDM.

HUMAN STUDIES

In 1984 the initial observation published linking infant feeding practices and the later development of IDDM involved an ecological study of breast-feeding practices over several years in Scandinavia. The study showed that children born during years when breast-feeding was common were less likely to develop IDDM compared with those born during years when breast-feeding was less popular. These findings inferred that either the absence of breast-feeding or the early introduction of cow's milk formula to the infant's diet were factors in the development of IDDM in genetically susceptible individuals.²⁶ Since then over 90 articles have been published, both defending the original concept and presenting arguments against its validity. Gerstein,²⁷ in a meta-analysis, reviewed all the publications and carefully selected about 20 studies that met stringent scientific criteria. This analysis concluded that there was a modest, but statistically significant association (odds ratio ≥ 1.5) between the early introduction of cow's milk (and/or early termination of breast-feeding) and the development of IDDM in childhood. The timing, dosage, and duration of the infant's exposure to cow's milk may be important, with some studies suggesting earlier age of onset of IDDM in those who were not breast-fed or had very limited exposure to human milk.²⁸⁻⁴⁵

A commentary by Kostraba⁴⁶ accompanying the Gerstein meta-analysis appropriately broadens the

The recommendations in this statement do not indicate an exclusive course of treatment or procedure to be followed. Variations, taking into account individual circumstances, may be appropriate.

PEDIATRICS (ISSN 0031 4005). Copyright © 1994 by the American Academy of Pediatrics.

discussion to include other aspects of infant feeding and suggests caution in moving from statistical relationships to causation. If a causal link exists between the ingestion of cow's milk and the onset of diabetes, it seems that milk protein or some subfraction is an active precipitator of the autoimmune process in genetically susceptible subjects, rather than human milk providing a protective influence. There is no evidence that processed milk, such as that found in commercial infant formulas, is in any way more or less harmful than whole cow's milk.

It has been known for several years that children with IDDM have an increased frequency of antibodies to a variety of cow's milk proteins, which is particularly evident in those with early onset IDDM. The recent article by Karjalainen et al²⁵ extends these observations and may provide additional insight into the initiation of the autoimmune process. These investigators identified antibodies to a 17-amino acid fragment of bovine serum albumin in 100% of a large group of Finnish children with newly diagnosed diabetes. Bovine serum albumin, which is present in cow's milk, is immunologically distinct from human serum albumin with little or no cross-reactivity. Antibodies to the 17-amino acid bovine serum albumin peptide molecule were found in few healthy controls or siblings of diabetic children. These exciting, provocative results have not been fully duplicated in extended studies in the initial laboratory and have yet to be confirmed by other investigators.⁴⁷

ANIMAL STUDIES

To our knowledge, the first documentation of a link between cow's milk protein and diabetes in susceptible animal strains was reported in 1984, shortly after the Scandinavian observations of breast-feeding practices and the development of IDDM.^{26,48} The addition of cow's milk protein to routine rat chow increased the frequency of diabetes in genetically susceptible biobreeding (BB) rats up to nearly 100%. Removing all whole protein and replacing it with a protein hydrolysate reduced the expression of diabetes in these animals to nearly zero. Numerous studies of feeding have since been carried out utilizing primarily the genetically susceptible BB rat and nonobese diabetic mouse strains. Although many studies have confirmed a provocative effect of milk proteins and beef proteins on the frequency of diabetes,⁴⁹⁻⁵³ this finding has not been invariably true. Several investigators have been unable to replicate the early findings consistently and have in some cases identified evidence that a number of plant proteins, most notably soy, may also trigger diabetes in susceptible animal strains.⁵⁴⁻⁵⁹

CONCLUSION

1. Insulin-dependent diabetes mellitus develops within a group of individuals who carry specific diabetes susceptibility traits. Because all of the potential diabetes "susceptibility genes" are not known, currently it is not possible to identify all individuals at risk. It appears, however, that a small percentage of such individuals will ever develop clinical diabetes mellitus.

2. The autoimmune destructive process may be triggered by a number of environmental events.
3. Early exposure of infants to cow's milk protein may be an important factor in the initiation of the β cell destructive process in some individuals. It is not known whether the cow's milk protein in commercially available infant formulas is associated with this process.
4. The avoidance of cow's milk protein for the first several months of life may reduce the later development of IDDM or delay its onset in susceptible individuals.
5. Research directed toward further defining the possible relationship between infant feeding practices and the development of IDDM is needed.

RECOMMENDATIONS

1. Breast-feeding is strongly endorsed as the primary source of nutrition during the first year of life for all infants.
2. In families with a strong history of IDDM, particularly if a sibling has diabetes, breast-feeding and avoidance of commercially available cow's milk and products containing intact cow's milk protein during the first year of life are strongly encouraged.
3. Since the antigenicity of infant formulas and cow's milk may be different and there is no evidence against the use of formula for infants whose mothers do not breast-feed, commercial infant formulas utilizing cow's milk protein remain the approved alternate.
4. The substitution of soy-based formulas for milk-based formulas is not advised for either general or high-risk infant feeding practices because of animal studies linking the ingestion of soy protein intake to the development of diabetes.
5. The substitution of elemental formulas for milk-based formulas has intellectual appeal as potential antigenically harmful large proteins have been replaced by dipeptides, tripeptides, and oligopeptides. However, because no scientific studies in humans confirming their benefit are yet available, this feeding option cannot be endorsed.
6. A prospective randomized trial in which genetically susceptible infants avoid the ingestion of cow's milk should be developed through collaborative national and international arrangements.

WORK GROUP ON COW'S MILK PROTEIN AND DIABETES MELLITUS

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Pediatrics 1994;94;752

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