

MINIREVIEW

Diet, Autoimmunity, and Insulin-Dependent Diabetes Mellitus: A Controversy (43897C)

CAROLYN D. BERDANIER¹

Department of Foods and Nutrition, University of Georgia, Athens, Georgia 30602

Abstract. Insulin-dependent diabetes mellitus (IDDM) is a serious disorder comprising approximately 10% of the total diabetic population. The majority of the genetic mutations that result in the phenotypic expression of the IDDM genotype are in the immune system. In some, the disease arises as a consequence of a viral infection. While some viruses target the islet β cell and destroy it, other viruses induce changes in the antigen recognition system such that the affected individual appears to have autoimmune disease. Autoimmune-IDDM results from one or more mutations in the immune system that result in a failure to distinguish self antigens from foreign antigens. As a result, the β cells of the endocrine pancreas are destroyed. This review addresses the issue of whether dietary factors, in particular, milk protein, can initiate the autoimmune process. Based on the population studies available in the literature, the conclusion is reached that, while antibodies to milk proteins can be found in the patient with autoimmune diabetes mellitus, these antibodies were probably elicited by a closely related protein (antigen mimicry). Because one of the features of autoimmune disease is a loss of antibody specificity, cross-reactivity occurs and appears to identify milk protein(s) as the antigen.

[P.S.E.B.M. 1995, Vol 209]

Diabetes mellitus is a collection of disorders having in common an abnormal glucose-insulin relationship. In its most severe form, it is characterized by hyperglycemia, ketosis, polyurea, polydipsia, tissue wasting, and rapid weight loss. If unrecognized and untreated, death will ensue. Milder forms of disordered glucose tolerance also exist and a variety of symptoms and secondary complications have been described (1, 2). Because of the tremendous variability in disease characteristics and consequences, scientists through the years have tried to de-

velop subcategories of diabetes. This has aided our understanding of the pathophysiology involved.

The American Diabetes Association has estimated that one person in 14 either has or will develop one of the many forms of diabetes in his/her lifetime. Of this population, about 90% will develop the disease in mid to late life. These people will be able to manage their disease through diet and exercise and may have no need for insulin supplementation. These people are said to have non-insulin-dependent diabetes mellitus (NIDDM) because they usually can manage their disease without daily insulin injections.

In contrast, there is a small group of people for whom daily hormone replacement is absolutely required, a condition referred to as insulin-dependent diabetes mellitus (IDDM). These patients differ in many ways from those with NIDDM. The age of onset is usually much earlier, and the disease is more severe and more difficult to manage. Secondary complications are more frequent and severe in the IDDM pa-

¹ To whom requests for reprints should be addressed at Department of Foods and Nutrition, University of Georgia, Athens, GA 30602.

tient than in the NIDDM patient. In both IDDM and NIDDM, the role of genetics is quite strong. Studies of identical twins (1–3) have resulted in an estimate of concordance of nearly 100% for NIDDM and between 30% and 60% for IDDM.

The age of onset of IDDM is frequently less than 15 years. The incidence of IDDM varies widely throughout the world. Table I shows some incidence rates in several countries for children younger than 15 years old (4). Within these countries, there can be areas where the incidence is higher or lower than shown in this table. There are year-to-year variations as well. As mentioned, concordance for IDDM in identical twins varies. This implies that environmental factors may play a strong and independent role in disease development. Dietary ingredients, viral infections, and exposure to toxins are among the factors that influence IDDM development. The purpose of this review is to address the question of whether dietary milk protein can trigger IDDM in children. Before this question can be addressed, a brief review of the role of the immune system in the pathophysiology of IDDM is in order.

IDDM and The Immune System

Living animals respond to a large number of antigens by producing antibodies. This is a normal physiologic process. There is a considerable difference between antibody production and autoimmune disease (5). As Weiner *et al.* (5) have pointed out in a recent review of autoimmune disease, autoimmune diabetes mellitus can be accompanied by a number of endocrine failures. Polyendocrinopathy is not uncommon. In addition, there is immune tolerance which is particularly difficult to break. By immune tolerance, we mean that the individual will tolerate a range of intakes before a systemic immunologic response is elicited. Localized responses such as gluten induced enteropathy (local reaction of enterocytes to dietary gluten resulting in diarrhea) are not included in the term, immune tolerance, and should not be confused with diseases of the immune system. Similarly, food intolerances should not be confused with food components that suppos-

edly induce or trigger an autoimmune response. These are two different processes. While the former has been well documented, the latter has not. This review addresses the concern that milk proteins could elicit or trigger autoimmune diabetes mellitus.

IDDM results when the pancreas fails to release sufficient insulin to facilitate glucose use. This failure is due to the destruction of the β cells in the islets of Langerhans. Islet destruction can be the result of a toxin such as lead or to a viral infection or to an autoimmune reaction. While IDDM due to a toxin is relatively rare, destruction of the islets by a virus and by the autoimmune process occurs more commonly. These two causes of IDDM are summarized as follows:

Viral Diseases

Epidemiologists have noted that, following epidemics of diseases such as flu (influenza), there are upsurges in the number of people with newly diagnosed IDDM (4, 6). Not all people who contract flu develop IDDM, nor have all people who develop IDDM had their disease preceded by flu. Other infections (i.e., Coxsackie B or encephalomyocarditis viruses) can also precede IDDM. Certain strains of mice have been found to develop IDDM following exposure to these and other closely related viruses (7–12). The picornaviruses, which include several strains of encephalomyocarditis virus, the foot-and-mouth disease virus, and a number of Coxsackie B viruses, can persist in susceptible animals. These persistent infections can cause damage in addition to the typical lytic effect that occurs during the acute phase (13). Damage can take the form of producing (or inducing) small changes in cell proteins that change the function of the protein and/or change the recognition of this protein as a normal cell constituent. These slightly modified self proteins then are recognized as foreign and an antibody is produced to destroy it. One such protein is the islet cell surface protein (ICS). Antibodies to ICS have been found in virally infected animals and humans. Viruses also induce the production of cytokines such as interferon, the interleukins, and tumor necrosis factor. These substances alter the immune response by regulating the expression of β -cell antigens and thus contribute to the development of insulinitis (inflammation of the islet cells). The mechanisms whereby viruses induce IDDM have been the subject of considerable speculation (8–18). A current supposition is that susceptibility to IDDM subsequent to a viral infection has a genetic component. In those rodents genetically prone to IDDM, infection with the encephalomyocarditis virus or the Coxsackie B virus is followed by IDDM but not in rodents that do not have a genetic tendency to develop diabetes. This suggests a genetic linkage between the genes that encode the components

Table I. Age-Specific Incidence Rates of IDDM in Children Less Than 15 Years of Age

Finland	35.3/100,000
Denmark	21.5/100,000
USA	14.3/100,000
Malta	13.6/100,000
United Kingdom	13.5/100,000
Australia	13.2/100,000
Netherlands	11.0/100,000
New Zealand	10.1/100,000
Algeria	8.1/100,000
Japan	1.8/100,000

(From Karvonen *et al.*, 1993 [4]).

of the immune system (10, 14) and the genes that encode the components of the glucose stimulated insulin response system in the pancreatic β cell. Such variability and linkage in rodents is likely matched in humans and explains why some humans develop IDDM subsequent to viral infections while others do not.

Notkins *et al.* (8, 12, 16, 18, 19) have suggested that susceptibility to viral-induced islet cell destruction is compatible with a single gene acting in an autosomal recessive manner. It is proposed that the mode of action of such a gene would be to control the membrane proteins that recognize the virus as an antigen and signal the production of antibodies to this antigen. Others (9, 11, 12, 14) have proposed that there are genetic differences in membrane permeability which, if altered, would permit entry of the viral DNA into the β cell. The viral DNA would supplant the β cell DNA and destroy it. Studies using fluorescein labeled viral antibodies have provided support for this mechanism (9, 11, 12, 14). Such studies have shown that these viruses enter the β cell and in particular, that the Cocksackie B virus can induce a change in β cell DNA (9, 14). A study of 250 children (20), who died as a result of a variety of acute viral infections and who had a variety of symptoms, revealed that seven died with Cocksackie B infection. Of these seven, four had significant β -cell destruction. Had these children survived the acute phase of their infection, no doubt they would have developed IDDM.

Autoimmune Disease

Perhaps more common than a viral infection as a cause of IDDM is autoimmune disease. Autoimmune disease is a broad category of diseases which includes not only IDDM but also thyroiditis, psoriasis, and rheumatoid arthritis. Autoimmune disease can result when mutations in the genes that encode the various components of the immune system occur and the body's own protein is recognized as an antigen. IDDM due to autoimmune disease occurs when the autoimmune reaction results in destruction of the β cell in the islets of Langerhans. This destruction appears associated with a gene or genes within the major histocompatibility complex, MHC (21). This complex is approximately 2×10^6 nucleotides and contains more than 100 different genes, any one of which could be aberrant and be responsible for a particular form of autoimmune disease. The genes for MHC are located on Chromosome 6. Several forms of IDDM in mice have been mapped to this chromosome (11, 14). Recently, Marchalonis *et al.* (22) reviewed the autoimmune process and its role in autoimmune diseases. The reader is referred to this work for the details of this process.

The development of autoimmune IDDM is associated with an inflammation of the pancreatic islet cells (insulinitis). CD4 and CD8 T cells, B cells, macro-

phages, and killer T cells have all been found in inflamed islet cells in humans, NOD mice, and BB rats (23–32). NOD mice and BB rats are frequently used to study the development of autoimmune IDDM. The diabetic trait is observed during puberty (60–90 days of age), and, if untreated, the animal dies. The IDDM in NOD mice can be prevented or delayed with the inclusion of 1,25-dihydroxyvitamin D (an immunosuppressant) supplements in the diet (33), with feeding insulin (34), feeding a protein free diet, alternate-day feeding, vitamin E supplements, and raising the ambient temperature (35, 36). Feeding milk proteins to NOD mice results in IDDM development as does feeding the mice a standard “chow” type diet. Some of these “chow” type diets have a milk protein constituent. The amount and kind of milk protein used is variable but the case has been made that this “chow” constituent elicits a response similar to that elicited by a semi purified diet containing casein or lactalbumin. However, the percent protein in the “chow” type diet provided by milk protein is quite small compared with that provided by the plant proteins (from corn, oats, wheat, etc.). It should be noted that both NOD and BB rats are endogenously infected with retroviruses (13). While the role of these viruses in IDDM is unclear, it is apparent that IDDM will not develop in these rodents without them. These viruses have been shown to be clustered in the β cells of these animals and found associated with the insulinitis that precedes the diabetic state (13).

When milk-based diets are used, anti-bovine serum albumin (BSA) antibodies have been found (37). It is not likely that BSA, a very expensive protein, was used as a diet ingredient. More likely is the possibility that these antibodies reacted to BSA because the protein was similar to another protein to which these antibodies were raised. This is a case of mistaken identity or antigen mimicry.

Autoimmune IDDM in BB rats has been prevented by cyclosporin (38), total lymphoid irradiation (39), thymectomy (40), early insulin treatment (41), high-protein diets (42), vitamin E supplements (43), a casein-based diet (44), and a diet containing a mix of amino acids instead of intact protein (45). IDDM development is enhanced by feeding a gliadin based diet, a skim milk diet, or the standard “chow” (45). As can be seen, a variety of experiments have been conducted in the rodent models and the results are, in some instances, conflicting. In part, these conflicts might be due to the animal used.

In humans with autoimmune IDDM, islet cell antibodies to cytoplasmic antigens have been reported as early as 1974 (30). Following this initial report, hundreds of antibodies have been found in humans with IDDM. Glutamic acid decarboxylase (GAD), an enzyme found in β cells that catalyzes the synthesis of

the neurotransmitter, γ aminobutyric acid (GABA), has been shown to be an antigen in autoimmune IDDM (45–56). β cells, like neuronal cells, possess a mechanism for insulin release that depends on a specific tropic stimulus. GABA and GAD are important components of this secretion signaling system as are a glucose transporter (GLUT) and several other enzymes. Autoantibodies to GAD have been observed prior to the development of the clinical state (46–49) and the presence of these antibodies has been suggested as an early indication of autoimmune IDDM (47). These antibodies have also been found in islets from BB rats (49). In both rats and humans, GAD has been cloned and characterized (50–52) and in humans GAD has been mapped to Chromosome 10 (51). Actually, two isoforms (65-kDa and 67-kDa GAD) have been isolated, and each are encoded by a single gene.

While GAD antibodies can indicate incipient IDDM, these antibodies are also elevated in other autoimmune diseases (in the absence of diabetes), yet in each disease there are distinct differences in epitope recognition (53, 56). This suggests that the autoantigen is being presented to the T cells and B cells by different mechanisms.

Over the last two decades, a plethora of islet cell autoantigens have been reported. Some of these are listed in Table II. So many have been reported that it has become difficult to determine which are causal and which are the result of the disease process. For example, islet cell antibodies to plasma borne C-peptide have been reported in adults having diabetes for at least 10 years (55). Antibodies to insulin have been found in newly diagnosed children but not in their high risk relatives (57). As mentioned above, GAD antibodies have been found in humans and rodents prior to IDDM diagnosis. Insulin receptor antibodies as well as antibodies to a small peptide called Hsp65 and several others listed in Table II have been reported. Of interest in this review, is the report that antibodies to bovine serum albumin (BSA) and a small 17 amino acid precursor peptide called ABBOS unique to BSA have been reported. The finding of these antibodies created a flurry of studies designed to determine whether a linkage exists between the intake of milk and the development of autoimmune IDDM. Concern was expressed about the practice of feeding formulas based on cows milk to infants and whether antibodies to components of cows milk could serve as a trigger for IDDM (58). There are several reports in the literature that address this issue. These are discussed in the following section.

BSA and ABBOS as Antigens in IDDM

Despite intensive study of the HLA system and the identification of a variety of HLA markers that are associated with an increased risk for IDDM, the ge-

Table II. Autoantigens That Elicit Islet Cell Antibodies in Humans and Rodents Manifesting Autoimmune IDDM

Autoantigen	Comments
Sialoglycolipid	Stimulates ICA
Glutamic Acid Decarboxylase (GAD)	Antibodies present before clinical state develops
Insulin (58,000 kDa, 51 amino acids)	Antibodies found after diagnosis
Insulin receptor 38,000 M _r	Antibodies found after diagnosis Antibodies develop in patients with insulinoma
Hsp 65	A 24 amino acid peptide that elicits antibodies in NOD mice
RIN polar	Antibodies are related to those formed in response to certain gangliosides
GLUT	
BSA 52,000 M _r	Antibodies present before clinical state develops. Likely the same as GAD
Carboxypeptidase H	Cell surface autoantigen and a major protein in insulin secretory granules
ICA 12/ICA 512 PM-1 60,000 M _r (humans)	Putative islet cell antigens Identical to Hsp 65 in mice; may be a polyclonal activator of autoreactive T cells
IAAb (anti α IgAb)	Anti-immoglobulin antibodies appear prior to IDDM
C-peptide	Antibodies found after IDDM diagnosis
ICA 69	Antibodies found prior to IDDM development

netic approach to determining causal factors has not been completely successful. Genetic factors alone cannot explain why siblings in the same family or twins are discordant with respect to IDDM. As mentioned, some of this discordance could be explained by differential exposure to viruses that could damage the insulin-producing islet cells. However, researchers have sought other explanations as well. In 1984, Christy *et al.* (59) reported that Norwegian children who were breast fed had a significantly reduced risk of subsequently developing IDDM than children who were formula fed and that the duration of breast feeding also affected IDDM. Those infants who were breast fed for more than 3 months had a smaller risk for IDDM than those who were breast fed less than 3 months. Similar findings with respect to a variety of food intolerances and breast feeding have also been noted (58). A Finnish study (60) reported that early exposure to unmodified cows milk elicited antibodies to the cows milk proteins. Some of these antibodies (IgM and IgA) also appeared in infants who had been exclusively breast fed. If these antibodies were elicited by cow's milk

proteins, it would mean that in the exclusively breast fed infant, cow's milk proteins consumed by the mother passed undigested from her intestine to her mammary gland and into her milk and served as antigens in the infant. This is highly unlikely. Food proteins rarely cross the mature enteral barrier intact. Furthermore, if such large proteins did cross, it is likely that these proteins would elicit an antibody response in the mother as these would be foreign proteins. More likely is the possibility that the antibodies that were found in the infant were those that cross-reacted with BSA and ABBOS. In other words, there was a loss of specificity by IgA and IgM in these infants. Hahn-Zoric *et al.* reported (61) the presence of specific IgG, IgA, and IgM antibodies in newborn unsuckled infants. The mothers of these infants were hypogammaglobulinemic. Some of the infants had antibodies that were totally lacking in the mothers. How this came about is not known. It has been suggested that IgG serves as a master antibody that stimulates the production of IgA and IgM in these infants and perhaps other infants as well. This suggestion counteracts the above in that these antibodies could not have been due to either the mother or infant's ingestion of cow's milk. However, normal and preterm newborns do absorb proteins present in their mother's milk (62). With age, gut closure occurs and these proteins are excluded. Likely, individuals differ in the age at which this closure occurs. In some, closure might occur shortly after birth; in others, closure may not occur for several months. In infants with delayed gut closure, a variety of food allergies may be observed (63). Such infants may have an allergic response even to their mother's milk proteins (64). Very few proteins in the mother's diet are found in the mother's milk. Those that do must escape enteric digestion and must cross many membranes in the mother in order to appear in the breast milk before they can serve as antigens in an infant with delayed gut closure. One such instance has been described (65). In this instance, not only was gut closure absent in the infant it was also absent in the mother. How else could her dietary proteins have crossed her gut barrier (as well as other barriers) to appear in her milk? This is probably a rare occurrence.

In another study, Dahlquist *et al.* (66) examined a variety of dietary ingredients and the risk of developing IDDM by children. In this Swedish study, food consumed by diabetic and nondiabetic children, age 0–14 years, was classified according to the content of protein, fat, carbohydrate (mono and disaccharides), nitrosamines, nitrates, nitrites, vitamin C, and fiber. The frequency of intake was evaluated as low, medium, and high, and the relative risk of developing IDDM was estimated from these frequencies. Significant linear trends for developing IDDM in response to

increasing frequency of intake were shown for solid foods containing high amounts of protein and nitrosamines. Milk as an entity was not a significant factor in IDDM risk. All of the above studies indicate or suggest that the milk proteins, whether in human or cows milk could be a source of antigens to newborns. Whether these proteins could be antigens and could stimulate or trigger autoimmunity is an entirely different question. Before this question is addressed, an examination of the composition of milk is in order.

Milk Composition

The composition of milk, particularly the protein component, is genetically controlled in man and domestic animals. Milk is a complex mixture of specific proteins, fats, vitamins, minerals, and carbohydrate. This mixture varies with the species (67). Interactions between the components create a complex microstructure which influences its nutritional value. Most of the protein in milk is synthesized by the mammary cell but some serum proteins such as albumin may be present in very small amounts. Shown in Table III are the major proteins in human and bovine milk. They are divided into two groups: caseins and whey proteins.

Caseins comprise a family of phosphoproteins and, in the bovine, represent ~80% of the total protein in the milk. There are considerable species differences in the amino acid sequences of these proteins, yet they have similar biophysical properties. Caseins interact with calcium and phosphate to form micelles or aggregates. The size of the aggregate is limited by κ casein, which coats the micelle and prevents further aggregation. κ casein has only one phosphoserine, whereas the other caseins have between 5 and 11 phosphoserines. κ casein is very soluble in calcium rich solutions and is the only casein that can be glycosylated and polarized.

Large numbers of proteins are found in whey. The major whey proteins in bovine milk are β lactoglobulin

Table III. Proteins in Human and Bovine Milk

	Human (g/liter)	Bovine
Caseins		
a_{s1}	0.4	10
a_{s2}	—	3.4
β	3	10
κ	1	3.9
Whey proteins		
α lactalbumin	1.6	1
β lactoglobulin	0	3
Serum albumin	0.4	0.4
Lysozyme	0.4	Trace
Lactoferrin	1.4	0.1
Immunoglobulin	1.4	0.7

Note. See Ref. 48 for more details on milk composition.

and α lactalbumin. In cows, the most abundant of whey proteins is the β lactoglobulin. β lactoglobulin is not found in human milk. Lactalbumins are synthesized in the mammary cell. Lactalbumins function in the transport of retinal in milk, which accounts for the fact that milk is an excellent dietary source for this vitamin. In addition, α lactalbumin is involved in the synthesis of lactose. α lactalbumin modifies the action of galactosyl transferase to facilitate the formation of lactose from galactose and glucose. Galactosyl transferase catalyzes the glycosylation of proteins in non-mammary cells. There is a small amount of serum albumin in milk and a considerable homology in the amino acid sequence of bovine and human albumin. Less than 20% of the total amino acids in albumin differ between the species. Albumin consists of repetitive domains that are duplicated nine times. Reactive groups (i.e., amino acids containing reactive molecules in their structures) are identical between the species (68).

Milk as a "Trigger" for IDDM

The homology in albumin between species raises questions about the proposal of Karjalainen *et al.* (58) that bovine serum albumin, or, more specifically, a 17 amino acid sequence called ABBOS, might serve as a trigger for the autoimmune sequence that culminates in IDDM. These investigators hypothesized that the ABBOS peptide is immunogenic only in hosts with the diabetes-associated HLA Class II (DR/DQ) haplotype able to bind and present this antigen. They also hypothesized that ABBOS and p69 (another antigen; see Table II) share a common epitope and that p69 could potentiate ABBOS-specific immune memory even after gut maturation. Karjalainen *et al.* studied 142 Finnish children with newly diagnosed IDDM and compared them with healthy age- and sex-matched children, and with adult blood donors. Anti-BSA antibodies and IgG antibodies to casein and β lactalbumin were determined. The diabetic children had elevated levels of IgG antibodies, which included antibodies directed towards ABBOS, BSA, casein, and β lactalbumin. This group subsequently (69) designed an intervention trial directed towards the determination of whether avoidance of cow's milk the first 6 months of life will prevent the development of IDDM in susceptible children. As yet, the results of this trial are not available; however, there are several points to consider when the results are complete. First, the Finnish people have one of the highest incidences of IDDM in the world (Table I). They also have high incidences of other genetic diseases. This is probably due to the relatively small and, in places, remote population groups. The population is thus quite likely to have a greater degree of homozygosity with respect to their gene pool than many of the other nations listed in

this table. Second, it is common for Finnish women to breast feed their infants for more than six months. If early exposure to cow's milk is a trigger for IDDM development, this is not the usual experience for the Finnish infant. Lastly, recall that IgG can serve as both an antibody and an antigen stimulating the production of IgA and IgM in infants (61). In a case-controlled study of Finnish children with or without IDDM, those who were less than 2 months of age when introduced to dairy products had a higher risk for developing IDDM than those who were older than two months when first exposed to dairy foods (70). A study (71) in Colorado, also using the case-controlled method, reached somewhat different conclusions. These workers found that IDDM risk for susceptible children was not only associated with cow's milk ingestion but also with the ingestion of a variety of solid foods.

In contrast to the results of the Finnish workers, Atkinson *et al.* (72) studied autoimmune IDDM subjects and subjects with other types of autoimmune diseases. Using an *in vitro* assay for antibodies to BSA or ABBOS. They found a positive response in 2 of 24 patients with IDDM, 1 of 25 first degree relatives of patients with IDDM who were negative for islet cell antibodies, 2 of 30 first degree relatives of patients who were positive for islet cell antibodies, and 1 of 29 normal subjects. Of the patients with nondiabetes autoimmune disease, 10%–31% had anti-BSA antibodies. The conclusion of these workers is based on theoretical considerations and antigenic mimicry. In this context, strong data to show that indeed there is significant cross-reaction between antibodies raised to human and bovine albumin are needed. These workers concluded that the presence of anti-BSA antibodies reflect a general defect in the immune system that could not distinguish individual antigens and thus developed antibodies that reacted to a group of similar antigens. As mentioned, human and bovine albumins are very similar in amino acid sequence. An antibody to one most likely would cross-react with the other.

While population studies have suggested a link between diet, particularly dairy products, and autoimmune IDDM, proof of this has not been provided. Cause-and-effect data cannot be collected for obvious reasons. Nonetheless, it is clear that the autoimmune disease that results in the destruction of the insulin producing β cells in the islets of Langerhans results in a severe form of diabetes mellitus. Whether specific dietary ingredients can activate the autoimmune process has not been shown. Although a variety of antibodies have been reported, no specificity for humoral immunity to dairy proteins has been shown. Thus, antibody responsiveness is not the disease but a characteristic of the disease. Even in rodent models (the NOD mouse, the BB rat) of autoimmune IDDM, this

specificity cannot be shown. These models will develop IDDM when fed a variety of special diets including both plant and milk proteins and their diabetes can be delayed by a variety of dietary and nondietary maneuvers. Thus, the question of whether the consumption of milk can have negative effects on subsequent IDDM development has been answered in part. Based on the Finnish, Scandinavian, and Colorado studies, it would appear that prolonged breast feeding (>6 months) is a benefit to children at genetic risk for autoimmune disease. However, it does not appear that cow's milk proteins (one or all) have a causal role in the autoimmune process that results in IDDM.

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