Infant feeding and the risk of type 1 diabetes[1–4]

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ABSTRACT

Type 1 diabetes is generally considered to be a chronic, immune-mediated disease with a subclinical prodrome during which β cell autoimmunity becomes overt disease at a variable rate in genetically susceptible individuals. Accumulated evidence supports a critical role of environmental factors in its development. Prospective birth cohort studies show that the first signs of β cell autoimmunity may be initiated during the first year of life. This implies that risk factors for β cell autoimmunity and type 1 diabetes must be operative in infancy. Early nutrition provides essential exogenous exposures in that period. This article discusses the role of factors related to infant nutrition in the development of β cell autoimmunity and type 1 diabetes and the potential mechanistic pathways involved. So far, no specific dietary factor has been shown to be an unequivocal risk factor for β cell autoimmunity or type 1 diabetes, and there are a number of contradictory observations with regard to the effect of various foods. This may reflect geographic and cultural differences in infant-feeding practices. Most studies suggest that the early introduction of complex foreign proteins may be a risk factor for β cell autoimmunity, and a pilot intervention trial has implied that weaning to a highly hydrolyzed formula may decrease the risk of β cell autoimmunity. Lack of vitamin D supplementation and accelerated growth might increase the risk of type 1 diabetes. Additional work, which includes the application of modern approaches such as metabolomics and epigenomics, is needed to discern the contribution of dietary factors in infancy to the diabetic disease process. *Am J Clin Nutr* 2010;91(suppl):1506S–13S.

INTRODUCTION

Type 1 diabetes is generally considered to be a chronic, immune-mediated disease with a subclinical prodromal period characterized by selective loss of insulin-producing β cells in the pancreatic islets in genetically susceptible individuals. Evidence supports the critical role of exogenous factors in the development of type 1 diabetes, such as *1*) the fact that <10% of those with *HLA*-conferred diabetes susceptibility do progress to manifest disease, *2*) a pairwise concordance of type 1 diabetes of <40% among monozygotic twins, *3*) a >10-fold difference in the disease incidence among whites who live in Europe, *4*) a several-fold increase in the incidence over the past 50 y in many industrialized countries, and *5*) migration studies that indicate that the disease incidence has increased in population groups who have moved from a low-incidence to a high-incidence region (1).

Accumulating evidence suggests that β cell autoimmunity may be induced early in life (2, 3). Data from the Finnish Type 1 Diabetes Prediction and Prevention (DIPP) Study have shown that the first autoantibodies may appear before the age of 3 mo as markers of the induction of the disease process (3). In addition, it has recently been reported that the increase in the incidence of type 1 diabetes among children in developed countries is most pronounced among children under the age of 5 y (4, 5). From the DIPP study we have learned that the overwhelming majority of those children who present with overt type 1 diabetes before the age of 10 y seroconvert to autoantibody positivity by the age of 2 y. Taken together these observations suggest that those exogenous factors that contribute to the initiation of the process that leads to type 1 diabetes must be operative in the first 2 y of life. Factors related to diet, such as intake of foreign proteins, fats, and vitamins, as well as growth, are strong candidates for such exogenous factors. We have previously reviewed possible nutritional risk predictors of β cell autoimmunity and type 1 diabetes (6). This review focuses on nutrition-related factors in the infant period more recently implicated as playing a role in the development of β cell autoimmunity and type 1 diabetes and discusses the potential mechanisms through which such factors might be involved in the diabetic disease process. The potential risk predictors of β cell autoimmunity and type 1 diabetes related to infant nutrition are listed in **Table 1**.

BREASTFEEDING AND COMPLEMENTARY FEEDING

Whether or not breastfeeding protects against type 1 diabetes is a controversial issue. There are studies that show a protective effect, no effect, or even a predisposing effect (6). Gerstein (7) performed a meta-analysis of retrospective case-control studies

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TABLE 1
Exposures related to infant nutrition that have been implicated as factors that predispose to or protect against β cell autoimmunity or type 1 diabetes[1]

Exposure (reference)	Outcome	Effect	Maximal effect size
Short breastfeeding (<3 mo), meta-analysis (7)	Type 1 diabetes	Predisposing	1.43 (1.15, 1.77)[2]
Early introduction of cow milk, meta-analysis (7)	Type 1 diabetes	Predisposing	1.63 (1.22, 2.15)[2]
Longer duration of exclusive breastfeeding (≥4 mo compared with <2 mo) (11)	β cell autoimmunity	Protective	0.17 (0.03, 0.86)[3]
Early introduction of cow milk (<2 mo compared with 2–3.9 mo) (11)	β cell autoimmunity	Predisposing	5.02 (1.27, 19.89)[3]
Early introduction of cow milk (<2 mo compared with ≥4 mo) (11)	β cell autoimmunity	Predisposing	6.19 (1.10, 34.84)[3]
Short duration of breastfeeding (<4 mo) (12)	β cell autoimmunity	Predisposing	2.09 (1.45, 3.02)[3]
Early introduction of cow milk (≤3 mo) (12)	β cell autoimmunity	Predisposing	1.84 (1.01, 3.37)[3]
Weaning to a highly hydrolyzed formula (TRIGR pilot) (20)	β cell autoimmunity	Protective	0.44 (0.20, 0.93)[3]
Early introduction of cereals (<3 mo of age) (9)	β cell autoimmunity	Predisposing	4.0 (1.4, 11.5)[3]
Early introduction of cereals (<4 mo of age) (8)	β cell autoimmunity	Predisposing	4.32 (2.00, 9.35)[3]
Late introduction of cereals (≤7 mo of age) (8)	β cell autoimmunity	Predisposing	5.36 (2.08, 13.35)[3]
Early introduction of fruit and berries (≤4 mo of age) (19)	β cell autoimmunity	Predisposing	1.82 (1.19, 2.79)[3]
Early introduction of root vegetables (≤4 mo of age) (19)	β cell autoimmunity	Predisposing	2.02 (1.03, 3.95)[3]
Use of cod liver oil during the first year of life (21)	Type 1 diabetes	Protective	0.74 (0.56, 0.99)[2]
Supplementation with vitamin D in infancy, meta-analysis (27)	Type 1 diabetes	Protective	0.71 (0.60, 0.84)[2]

[1] TRIGR, Trial to Reduce IDDM in the Genetically at Risk.
[2] Odds ratio; 95% CI in parentheses.
[3] Hazard ratio; 95% CI in parentheses.

available in 1993, which showed that short-term breastfeeding (for <3 mo) was associated with an increased risk of type 1 diabetes, with an odds ratio (OR) of 1.43. Most prospective studies that have explored the association between breastfeeding and the emergence of β cell autoimmunity have reported that breastfeeding has no effect (8–10). However, a couple of studies have indicated that short-term breastfeeding is a risk factor for the appearance of signs of β cell autoimmunity (11, 12). There may be reasons for the contradictory findings with regard to the effect of breastfeeding on the development of β cell autoimmunity and type 1 diabetes. Many studies have looked at overall breastfeeding without any differentiation between exclusive and total breastfeeding. In addition there are conspicuous differences in the breastfeeding practices between various countries.

Early introduction of cow milk proteins (ie, conventional infant formulas) has also been studied in relation to subsequent risk of β cell autoimmunity and type 1 diabetes. The introduction of infant formula reflects, in general, the mirror of the duration of exclusive breastfeeding. These studies have also produced contradictory outcomes (6); mainly, some surveys have indicated that early introduction of cow milk increases the risk of β cell autoimmunity (11, 12) and type 1 diabetes (13–15), whereas others have shown no association between those 2 phenomena (16, 17). The meta-analysis of case-control studies by Gerstein (7) implied that early exposure to cow milk proteins (<4 mo old) was a risk predictor of type 1 diabetes with an OR of 1.63. Early exposure to cow milk is related to shorter duration of breastfeeding. In a Finnish national case-control study (15), when both the duration of breastfeeding and the age at introduction of cow milk were studied, early exposure to cow milk turned out to be the dominant risk determinant of type 1 diabetes. Increased infant growth did not explain this association (18). Again there may be several explanations for the discrepant results. Although milk-based formula is, in most cases, the first complementary food an infant is exposed to in developed nations, there is variation between countries and cultures in the proportion of babies first introduced to milk-based formula. In addition there are international differences in the kind of complementary foods that infants who are not first exposed to milk-based formula are given. For example, a substantial proportion of infants in the United States are first given cereals, whereas this is extremely rare in Finland (8, 10). The use of partly or highly hydrolyzed formulas in normal infants varies considerably from country to country. This can be expected to be an important confounder when the association between the introduction of cow milk–based formula and the development of β cell autoimmunity and type 1 diabetes is analyzed.

To date, the only intervention trial of infant nutrition has been the pilot of the Trial to Reduce IDDM in the Genetically at Risk (TRIGR) (19). In this pilot 230 Finnish infants at increased risk of type 1 diabetes were randomized at weaning to either a highly hydrolyzed formula or a conventional cow milk–based formula before the age of 8 mo. The increased diabetes risk was based on a positive history of type 1 diabetes in a first-degree relative, and the participant had to carry an HLA genotype that conferred enhanced disease risk (19). During the intervention period the families were recommended to give no food products that contained cow milk or bovine serum albumin to their infants. The intervention resulted in a postponement of the introduction of intact cow milk proteins by several months in the active intervention group. After follow-up to a mean age of 4.7 y an interim analysis showed that the nutritional intervention in infancy resulted in a decrease in most signs of β cell autoimmunity in the range of 50–60%. After adjustment for the observed difference in the exposure time to the study formula there was a significant decrease in the cumulative incidence of both islet cell antibodies and positivity for at least 1 of the 4 autoantibody reactivities analyzed (19). This suggests that it may be possible

to manipulate spontaneous β cell autoimmunity by nutritional intervention during infancy.

Two prospective studies conducted in the United States and Germany have reported an association between the introduction of cereals in infancy and the emergence of early β cell autoimmunity (8, 9). The US report suggested that both early (before the age of 4 mo) and late (at the age of $\geq$7 mo) exposure to cereals were associated with an increased risk of β cell autoimmunity, whereas the German study implied that an increased risk was related to exposure to cereals before the age of 3 mo. In addition, the US survey indicated that both gluten-containing and non-gluten-containing cereals conferred an increased risk of β cell autoimmunity. Neither of these studies reported any data on the amount and type of cereals the infants were exposed to at various ages. Early exposure to cereals is against generally accepted recommendations on infant nutrition in all developed countries and occurs infrequently. For example, Finnish babies are rarely exposed to cereals before the age of 4 mo. A prospective analysis of data from the DIPP study showed no relation between early or late introduction of cereals and emergence of advanced β cell autoimmunity (10).

The DIPP study comprises a substantially larger birth cohort and includes a higher number of endpoints than any of the other birth cohort surveys that have reported data on the association between infant feeding and β cell autoimmunity. Our analysis based on the DIPP study showed that early introduction of fruit and berries, as well as roots, is associated with increased risk of advanced β cell autoimmunity (positivity for $\geq$2 autoantibodies out of 4 analyzed) (10). In contrast, no relation was observed between advanced β cell autoimmunity and duration of exclusive or total breastfeeding or age at introduction of cow milk.

Stene and Joner (20) reported in 2003 that the use of cod liver oil during the first year of life was related to a decreased risk of type 1 diabetes. Such an association could not be confirmed in a later study (21). Cod liver oil comprises high concentrations of both vitamin D and omega-3 polyunsaturated fatty acids. A case-cohort study based on the Diabetes Autoimmunity Study in the Young (DAISY) population indicated that the intake of omega-3 fatty acids between the ages of 1 y and 6 y was associated with a decreased risk of β cell autoimmunity, with a hazard ratio of 0.45 (95% CI: 0.21, 0.96) (22). Recently, a TrialNet-based pilot trial called the Nutritional Intervention for the Prevention of Type 1 Diabetes was initiated to test the feasibility of a full-scale trial to address the hypothesis that dietary supplementation with an omega-3 fatty acid (docosahexaenoic acid) during fetal life and in infancy will prevent β cell autoimmunity in infants with an increased risk of developing type 1 diabetes. Ninety-eight infants have been enrolled in the pilot trial and they will be observed up to the age of 4 y (23). Inflammatory mediators, which include cytokines, chemokines, eicosanoids, and C-reactive protein, will be measured, along with fatty acids in maternal and infant blood. Thus far, all families have remained in the study and compliance has been reported to be excellent.

VITAMIN D AND VITAMIN E

Some studies have implied that the lack of oral vitamin D supplementation in infancy increases the subsequent risk of type 1 diabetes (24, 25). The European case-control study (24) from 7 centers indicated that supplementation with vitamin D resulted in a decreased risk of type 1 diabetes, with an OR of 0.67 (95% CI: 0.53, 0.86). A Finnish birth cohort study (25) reported that regular high-dose supplementation with vitamin D in infancy (2000 IU/d at that time compared with 400 IU/d currently) was associated with a decreased disease risk, with an OR of 0.12 (95% CI: 0.03, 0.51), and even irregular supplementation was related to a lower risk when compared with no supplementation (OR: 0.16; 95% CI: 0.04, 0.74). Suspicion of rickets within the first year of life was linked to an increased risk of type 1 diabetes, with an OR of 3.0 (95% CI: 1.0, 9.0). A recent meta-analysis based on 5 studies concluded that vitamin D supplementation in early childhood is associated with decreased diabetes risk (Table 1) (26). A pilot study that assessed the feasibility of a trial to test the hypothesis that daily supplementation with 2000 IU of vitamin D_3 that started from the age of 1 mo in high-risk infants identified from the general population based on HLA-conferred disease susceptibility would decrease the risk of β cell autoimmunity and type 1 diabetes has been performed in Canada (27). The outcome of that study shows that such a trial is feasible. A Chinese intervention trial in patients with late-onset autoimmune diabetes reported that the daily use of 0.5 μg alphacalcidol (1α-hydroxyvitamin D) for 12 mo resulted in better preserved β cell function (28).

However, a few arguments speak against a critical role of vitamin D deficiency in the development of β cell autoimmunity and type 1 diabetes. One consideration is that there is a general recommendation that all young children should be supplemented with daily vitamin D drops in Northern Europe, the area with the highest incidence of childhood type 1 diabetes in the world, and this recommendation is implemented by $\approx$80% of the parents, at least up to the age of 1 y (29). In addition there are a few regions with a low incidence of type 1 diabetes in Northern Europe (eg, Russian Karelia) that had an annual incidence rate of 7.8/100,000 children under the age of 15 y in the time period 1990–99, compared with 42/100,000 in Finland (30). However, we observed no significant differences in the circulating vitamin D concentrations in pregnant women and schoolchildren between Russian Karelia and Finland (31).

Vitamin E is a fat-soluble vitamin of plant origin composed of 8 structurally related compounds and functions as a classic free radical scavenging antioxidant. Data obtained in nonobese diabetic mice, an animal model of autoimmune diabetes, have implied that vitamin E may have a protective effect against diabetes (32). However, we could not find any association between the circulating concentrations of α- or γ-tocopherol that started from the age of 1 y and risk of advanced β cell autoimmunity in the Finnish DIPP birth cohort study (33).

INFANT GROWTH

Increased weight gain in infancy has repeatedly been reported to be a risk factor for type 1 diabetes later in childhood (34). Finnish studies have shown that those children who presented subsequently with type 1 diabetes were not only heavier but also taller in infancy (18, 35), although there were no significant differences in birth weight or length. A recent survey showed that those subjects who presented with type 1 diabetes between 15 and 39 y of age had a higher gain in their body mass index during infancy than unaffected controls (36).

POTENTIAL MECHANISMS

In this section we discuss possible mechanistic pathways involved in predisposition to or protection against β cell autoimmunity and type 1 diabetes. These mechanisms are summarized in **Table 2**.

Breastfeeding

Several mechanistic pathways may be operative in the mediation of the potential protection against type 1 diabetes conferred by breastfeeding. Gut permeability decreases faster over the first months of life in breastfed infants compared with infants given conventional or partly hydrolyzed formulas (37). Early enterovirus infections have been implicated as a strong trigger candidate for β cell autoimmunity (1). We and others have shown that breastfeeding protects against enterovirus infections in the infant period (38, 39) and, accordingly, this would decrease the risk of enterovirus-triggered β cell autoimmunity.

Complementary feeding

Early introduction of cow milk proteins may induce mucosal inflammation and increased gut permeability. Several recent studies have suggested that patients with manifest type 1 diabetes have signs of intestinal inflammation. Westerholm-Ormio et al (40) reported enhanced expression of HLA–class II molecules, adhesion molecules, and proinflammatory cytokines in small intestinal biopsy samples from children with type 1 diabetes. Auricchio et al (41) observed higher density of intraepithelial CD3-positive and γ/δ T cells and lamina propria CD25-positive T cells, which reflected the activation of intestinal immunity in about one-half of their children with type 1 diabetes. Whether such intestinal inflammation is characteristic of children with preclinical type 1 diabetes remains questionable, but one may speculate that intestinal inflammation might represent an early immune aberration that predisposes to β cell autoimmunity and type 1 diabetes.

A series of studies has shown that children with newly diagnosed type 1 diabetes have increased concentrations of antibodies to dietary antigens and cow milk proteins in particular (42–44). Elevated circulating antibodies to cow milk proteins were reported in children with type 1 diabetes for the first time in 1988. Savilahti et al (42) observed that such children had significantly higher concentrations of serum immunoglobulin (Ig)A antibodies to cow milk and β-lactoglobulin and of IgG antibodies to β-lactoglobulin than age-matched controls. There are several alternative explanations for the enhanced humoral immune response to cow milk proteins seen in patients with type 1 diabetes. One is that increased consumption of cow milk before the presentation of clinical type 1 diabetes is a risk factor for the disease. Another could be that the immunologic reactivity to cow milk proteins may be enhanced in children who later present with type 1 diabetes, and a third alternative is that the gastrointestinal permeability to cow milk proteins might be increased in such children. The latter 2 options are supported by our recent observation from the TRIGR pilot study that those children who subsequently progressed to overt type 1 diabetes had elevated concentrations of IgG antibodies to β-lactoglubulin from 3 to 18 mo of age and IgA antibody titers to cow milk formula at the age of 9 mo (45). This finding indicates that either the immune response to cow milk proteins is dysregulated or the intestinal permeability is increased in infancy among those children who present with clinical type 1 diabetes later in childhood.

Insulin is an essential autoantigen in type 1 diabetes because it is the only β cell–specific autoantigen in postnatal life. Insulin autoantibodies (IAAs) are the first, or are among the first, autoantibodies to appear when the disease process that results in type 1 diabetes is initiated in young children (2, 3). Because cow milk formulas generally are the first and most common dietary source of foreign complex proteins that an infant is exposed to in industrialized countries, we set out to assess whether early exposure to cow milk formula results in an immune response to the bovine insulin present in formulas, which differs from human insulin by 3 amino acids, 2 in the A chain and 1 in the B chain. Our study showed that the infants who were breastfed exclusively at least up to the age of 3 mo had substantially lower IgG-class antibodies to bovine insulin at the age of 3 mo than did those who were exposed to formula before that age (50). All subjects were observed up to the age of 18 mo. The follow-up period showed that the IgG-class insulin antibodies started to

TABLE 2
Proposed mechanistic pathways for nutrition-related exposures during infancy that increase or decrease the risk of β cell autoimmunity and type 1 diabetes

Factor	Proposed mechanisms	Reference
Breastfeeding	Decreased intestinal permeability.	37
	Decreased frequency of early enterovirus infections.	38, 39
Early introduction of cow milk proteins	Inflammation in intestinal mucosa.	40, 41
	Dysregulated immune response to cow milk proteins.	42–45
	Increased intestinal permeability.	37
Early introduction of cereals	Inflammation in intestinal mucosa.	40, 46
Early introduction of fruit, berries, and root vegetables	Presence of toxic contaminants?	47
Weaning to a highly hydrolyzed formula	Postponed introduction of cow milk proteins that includes bovine insulin.	
	Decreased intestinal permeability?	
	Induction of regulatory T cells in gut-associated lymphoid tissue?	
	Increased diversity of gut microflora?	
Vitamin D deficiency	Decreased suppression of pathologic Th1 immune responses.	48
Accelerated infant growth	Induced β cell stress and insulin resistance.	49

slowly decrease after the age of 3 mo as a sign of the development of oral tolerance in those infants who were given formula before that age, whereas in those exclusively breastfed for at least the first 3 mo of their life, the concentrations of antibodies increased up to the age of 12 mo and thereafter leveled off. That antibody profile was expected because these infants were exposed to cow milk–based products, mostly formula, at some point during their first year of life. The study cohort included a small series of subjects (n = 11) who developed early signs of β cell autoimmunity. These infants showed concentrations of IgG antibodies to bovine insulin that increased continuously. This increase may be explained partly by the appearance of IAA because there is a substantial cross-reactivity between bovine and human insulin in the insulin antibody assays. However, the increase in IgG antibodies to bovine insulin remained significant, even after adjustment for the IAA titers. Our observation indicates that those young children who present with early signs of β cell autoimmunity appear to lack the capacity to develop oral tolerance to bovine insulin during infancy (50). Accordingly, the initial immune response to bovine insulin may later be diverted into a response that targets human insulin and the insulin-producing β cells in such individuals.

It has recently been reported that close to one-half of patients with type 1 diabetes have a proliferative T cell response to dietary wheat polypeptides, and that the cytokine profile of that response is principally proinflammatory (51). The positive T cell response to wheat polypeptides was associated with the *HLA DR4-DQ8* haplotype but surprisingly not with the *HLA DR3-DQ2* haplotype, which confers strong susceptibility to celiac disease. The authors interpreted their findings as a reflection of a diabetes-related inflammatory state in the gut immune system associated with defective oral tolerance and a possible gut barrier dysfunction. According to this observation, gluten is not responsible for the induction of the intestinal inflammation in type 1 diabetes. This is compatible with the finding in the US prospective study (8) in infants at risk of type 1 diabetes, that both gluten-containing and non-gluten-containing cereals confer increased risk of clinical disease. On the other hand it has been shown that patients with celiac disease are characterized by mucosal inflammation (40). In fact, the inflammatory state seems to be a more active process in patients with celiac disease. One recent study focused on the density and function of T cells in jejunal mucosa that express the transcription factor Foxp3 (forkhead box p3), perceived as a marker of regulatory T cells. In children with type 1 diabetes, the densities of Foxp3-positive cells were low and did not show activation of Foxp3 transcripts (46). This was in contrast to celiac disease, in which mucosal inflammation that involved Foxp3 expression was noted.

The mechanisms of action for the predisposing effect of the early introduction of fruit, berries, and roots on the emergence of β cell autoimmunity are not defined. One may speculate that such food items contain toxic contaminants (47). Bafilomycins and concanamycins are toxic plecomacrolide antibiotics characterized by a 16- or 18-member macrolactone ring. Bafilomycins are produced by *Streptomyces* species that can infest tuberous vegetables, potatoes, and sugar beet in particular. In potatoes, *Streptomyces* infection causes common scab disease, which presents as crusted lesions or pits on the surface of the tuber and occurs wherever potatoes are grown. The ability of *Streptomyces* spp. to infect vegetables and to produce bafilomycins provides an avenue for these toxins to enter the human diet, either directly or indirectly, because of toxin accumulation through the food chain. Australian investigators have shown that bafilomycins can accelerate the onset of autoimmune diabetes in the offspring of exposed nonobese diabetic mice (52). Cereulide toxin extracted from potatoes and milk has been shown to cause β cell destruction in fetal porcine islets (53).

One may ask why weaning to a highly hydrolyzed formula would protect against β cell autoimmunity. One alternative is that such an intervention postpones the introduction of intact cow milk proteins, which include bovine insulin. One may also speculate that a highly hydrolyzed formula might facilitate decreased intestinal permeability when compared with conventional or partly hydrolyzed formulas. One hypothesis is that a highly hydrolyzed formula may stimulate the maturation of regulatory T cells in the gut-associated lymphoid tissue, which leads to suppression of signs of β cell autoimmunity. A fourth option would be that the highly hydrolyzed formula could affect gut microflora that favor decreased microbial diversity, which may be associated with enhanced risk of autoimmune diabetes (VR Velagapudi et al, unpublished data, 2009).

Vitamins D and E

In addition to the role of vitamin D as a crucial player in calcium and bone metabolism, important immunomodulatory actions have been attributed to this hormone (48). The extensive presence of the vitamin D receptor (VDR) in the immune system and the expression of the enzymes responsible for the synthesis of the active vitamin regulated by specific immune signals suggest even a paracrine immunomodulatory role for 1,25-dihydroxyvitamin D_3. Vitamin D deficiency has been associated with an increased susceptibility to infections. Multiple macrophage functions essential for antimicrobial activity, such as chemotaxis, phagocytosis, and proinflammatory cytokine production, are defective in vitamin D–deficient mice. Moreover, vitamin D deficiency has been shown to be associated with an increased risk of Th1-mediated autoimmune diseases, such as inflammatory bowel disease, rheumatoid arthritis, systemic lupus erythematosus, and multiple sclerosis, as well as type 1 diabetes. This suggests that vitamin D deficiency leads to a decreased suppression of pathologic Th1-polarized immune responses.

Several studies have indicated an association between type 1 diabetes and polymorphism in the gene that encodes the VDR. However, a recent meta-analysis showed no evidence of any association between *VDR* gene polymorphism and type 1 diabetes (54). In contrast, Bailey et al (55) recently reported an association between type 1 diabetes and a polymorphism in the gene that encodes 1α-hydroxylase, the enzyme responsible for the second hydroxylation step, which results in active vitamin D. Accordingly, the possible association between vitamin D deficiency and type 1 diabetes and other immune-mediated disorders may be more complicated than previously assumed and may also be related to aspects other than vitamin D intake and circulating vitamin D concentrations. Vitamin D may also have a direct effect on islet cell function, because it has been shown that both 1α-hydroxylase and the VDR are expressed in rodent islets and human pancreatic tissue (56).

Free radicals have been implicated in the etiology of type 1 diabetes. Pancreatic islet cells are especially vulnerable to the toxic effects of free radicals (57). In insulitis that leads to β cell destruction, islet-infiltrating macrophages release free radicals, and β cell toxic cytokines and cytotoxic T cells may act via excessive formation of oxygen free radicals (58, 59). Both principal vitamers of vitamin E, α- and γ-tocopherol, provide antioxidant activities and, in addition, the latter has antiinflammatory properties (60).

Infant growth

Accelerated linear growth and weight gain result in an enhanced β cell load and increased insulin resistance (49). It has been shown experimentally that active β cells are more prone to cytokine-induced damage than are resting cells (61). Taken together these observations imply that rapid growth induces β cell stress. According to the accelerator hypothesis presented by Wilkin (62) some years ago, insulin resistance is an important factor that affects the rising incidence of both type 1 and type 2 diabetes. In such a scenario the only differences between these 2 forms of diabetes would be the pace of progression to overt disease and the fact that those who present with type 1 diabetes carry genetic susceptibility to autoimmunity.

OTHER ASPECTS RELATED TO INFANT NUTRITION

Recent data from the prospective Finnish DIPP study have shown that children who later progressed to type 1 diabetes had decreased serum concentrations of phosphatidylcholine at birth, decreased concentrations of triglycerides and antioxidant ether phospholipids throughout the follow-up period, and increased concentrations of proinflammatory lysophosphatidylcholine several months before seroconversion to autoantibody positivity (63). The lipid changes were unrelated to the child's HLA genotype. The metabolic profile was partially normalized after the seroconversion. If confirmed, these findings open up new avenues for nutritional intervention to start in the infant period, with the aim to compensate for the observed lipid deficiencies.

Epigenetics is the study of changes in phenotype or gene expression caused by mechanisms other than changes in the underlying DNA sequence. The former changes are in most cases environmentally induced. There is a series of dietary components associated with altered DNA methylation (64). These include folic acid, methionine, choline, genistein, and lycopene. In addition, the energy content and the proportion of various nutrients may have an effect on DNA methylation. It has been hypothesized that epigenetic changes in early life that lead to chromatin remodeling and regulation of gene expression underlie the developmental programming of obesity, type 2 diabetes, and the metabolic syndrome (65). Accumulated evidence suggests that the environment modifies the immune system through epigenetic mechanisms (ie, altered T cell DNA methylation) to induce systemic lupus erythematosus, which raises the possibility that epigenetics contributes to the development of other forms of autoimmunity as well (64).

CONCLUSIONS

Early nutrition represents one of the first environmental determinants to which an infant is exposed. Given that the first signs of β cell autoimmunity emerge during the first year of life in many subjects who later present with clinical type 1 diabetes, and that the most conspicuous increase in the incidence of type 1 diabetes has been observed among those diagnosed under the age of 5 y, it is likely that the disease process is initiated early in life in most cases. Accordingly, one should search among early exposures for those exogenous factors that trigger and drive the disease process. Although no specific dietary factor or nutrient in infancy has so far been shown to unequivocally play a role in the development of type 1 diabetes, there are data that indicate that dietary components may be risk factors that predispose to or protect against type 1 diabetes. Preliminary data suggest that weaning to a highly hydrolyzed formula cuts the cumulative incidence of β cell autoimmunity by the age of 5 y to about one-half, which provides evidence in favor of the possibility to nutritional modification of spontaneous β cell autoimmunity.

More research is definitely needed to confirm the contribution of early dietary factors to the development of β cell autoimmunity and overt type 1 diabetes. The mechanistic pathways have to be defined, and new approaches, such as metabolomics and epigenomics, have to be applied creatively and without any prejudice to facilitate progress in this area. It is important to identify early dietary elements involved in the disease process that results in clinical type 1 diabetes. The recognition of such determinants may provide measures for safe and effective primary prevention of type 1 diabetes aimed at the inhibition of the emergence of β cell autoimmunity either at the population level or in subgroups of individuals with increased genetic disease susceptibility.

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