Nutritional risk predictors of β cell autoimmunity and type 1 diabetes at a young age[1,2]

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ABSTRACT

Type 1 diabetes is an immune-mediated disease characterized by a preclinical prodrome during which β cell autoimmunity proceeds at a variable rate. Large geographic differences and a conspicuous increase in incidence, especially among young children since the 1950s, and the relatively low concordance in identical twins are factors that favor a critical role of environmental factors in the etiology of this disease. Only ≈5% or fewer subjects with *HLA*-conferred genetic susceptibility to type 1 diabetes actually develop the clinical disease. Breastfeeding, nicotinamide, zinc, and vitamins C, D, and E have been reported as possibly protecting against type 1 diabetes, whereas *N*-nitroso compounds, cow milk, increased linear growth, and obesity may increase the risk. Thus far, only the significance of infant feeding, cow milk, and vitamin D have been studied in both case-control and cohort settings. The major shortcoming of most studies done so far is that only single dietary exposures have been assessed at single time points. Putative nutritional and other confounding factors have received little attention as have the limitations of the dietary methods used. There is little firm evidence of the significance of nutritional factors in the etiology of type 1 diabetes. The availability of good markers of preclinical type 1 diabetes and of genetic risk have decreased the sample sizes needed and made longitudinal cohort studies of the assessment of children's diets feasible. *Am J Clin Nutr* 2003; 78:1053–67.

KEY WORDS Type 1 diabetes, preclinical diabetes, autoimmunity, β cell function, etiology, nutrition, growth

INTRODUCTION

Type 1 diabetes is perceived as a chronic immune-mediated disease with a subclinical prodrome characterized by selective loss of insulin-producing β cells in the pancreatic islets in genetically susceptible persons (1). Several lines of evidence support a critical role of environmental factors in the pathogenesis of type 1 diabetes. Studies in monozygotic twins suggest that only 13–33% are pairwise concordant for the disease (2, 3), which implies that there is either acquired postconceptional genetic discordance or differential exposure to putative environmental factors. The geographic variation in the incidence of type 1 diabetes in children is conspicuous even among whites, who have the lowest annual incidence in Romania (5/100 000 children aged < 15 y; 4) and the highest incidence in Finland (40/100 000 children in 1996; 5). > 350-fold worldwide difference in incidence rates has been observed (6). Such differences can hardly be explained by genetic factors. A considerable increase in the incidence of type 1 diabetes has been documented globally during the second half of the past century (4, 5, 7, 8), and, in Finland, the incidence has increased > 4 times from the early 1950s. Such a steep increase cannot be exclusively due to an enhanced genetic disease susceptibility in the population but must mostly reflect changes in lifestyle and environment.

Nearly 20% of the Finnish population have an increased *HLA*-conferred genetic predisposition to type 1 diabetes, whereas < 1% progress to having overt diabetes by the age of 20 y (9). Accordingly, only 1 of 20 subjects with enhanced *HLA*-defined disease susceptibility develops clinical type 1 diabetes, which supports a strong environmental impact on the risk of developing the disease. Various exogenous triggers, such as certain dietary factors and viruses, are thought to induce the immune-mediated process leading to extensive β cell destruction and ultimately to the clinical manifestation of type 1 diabetes (10, 11). In addition to their role as triggers, environmental factors may also have an accelerating or protective effect, thereby modifying the fate and the rate of the prediabetic process. This review discusses the role of nutritional factors that are potentially involved in the development of type 1 diabetes.

NATURAL HISTORY OF THE DEVELOPMENT OF TYPE 1 DIABETES

The clinical manifestation of type 1 diabetes represents end-stage insulitis, because at the time of diagnosis only a minority of the insulin-producing β cells are viable. The clin-

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Received March 25, 2003.

Accepted for publication May 29, 2003.

ical disease presentation is preceded by an asymptomatic period of variable duration (12). Aggressive β cell destruction may lead to disease manifestation within a few months in young children, whereas in others the process will continue for years, in some cases even for >10 y.

The appearance of diabetes-associated autoantibodies is the first detectable sign of emerging β cell autoimmunity. There are 4 disease-related autoantibodies that have been shown to predict overt type 1 diabetes (13). These include classic islet cell antibodies (ICA), insulin autoantibodies, and autoantibodies to the 65-kD isoform of glutamic acid decarboxylase and the tyrosine phosphatase–related IA-2 molecule (IA-2A). The number of detectable autoantibodies is unequivocally related to the risk of progression to clinical type 1 diabetes both in family studies and in surveys based on general population cohorts. Positivity for 3–4 antibodies is associated with a risk of developing clinical type 1 diabetes in the range of 60–100% over the next 5–10 y (14, 15).

Several studies have shown that β cell autoimmunity may be induced early in life (16, 17). In the Finnish Diabetes Prediction and Prevention (DIPP) Study population, the first antibodies appeared already before the age of 3 mo, and $\approx$4% of these children with increased *HLA DQB1*–conferred genetic risk developed at least one autoantibody by the age of 2 y, whereas 2.2% seroconverted to positivity for multiple (≥ 2) antibodies by that age. These numbers suggest that a higher proportion of the population develop signs of β cell autoimmunity rather than clinical type 1 diabetes. Data from the Finnish DIPP Study indicate that the spreading of the humoral autoimmune response from one epitope to another and from one antibody to another occurs in a relatively short time (12, 18). If such a spreading does not take place within 1 y after the appearance of the first autoantibodies, it is unlikely that it should occur later. These observations imply that positivity for a single autoantibody specificity represents in most cases harmless nonprogressive β cell autoimmunity, whereas the presence of ≥ 2 autoantibodies reflect a progressive process that only rarely reverts.

Accordingly, positivity for multiple autoantibodies can be used as a surrogate marker of clinical type 1 diabetes in prospective studies, particularly in young children, because the overwhelming majority of young children with multiple autoantibodies will eventually present with overt diabetes (19). The use of meaningful surrogate markers shortens the time needed for prospective studies on the pathogenesis of type 1 diabetes and for primary intervention studies aimed at preventing genetically susceptible persons from progressing to preclinical diabetes. The new insights into the natural history of type 1 diabetes have accordingly opened up new possibilities and strategies for assessing the role of environmental predictors, including nutritional factors in the development of diabetes.

There is a small male preponderance among children aged <15 y with newly diagnosed type 1 diabetes among white populations, but in those diagnosed after puberty there is a clear male excess with a ratio of 2 to 3:1 (20, 21). The reasons for such an abrupt switch in the sex ratio after puberty are not clear. Interestingly, Williams et al (22) reported recently that there is also an apparent male majority with signs of humoral β cell autoimmunity among first-degree relatives older than 10 y of age. Whether this change in sex ratio is related in any way to nutritional factors remains unknown.

HISTORICAL PERSPECTIVE

Interest in how nutritional factors such as different types of dietary fat and nicotinamide could modify the diabetogenicity of alloxan and streptozotocin in rodents began as early as the 1940s (23–25). However, research on the role of nutritional factors in the etiology of type 1 diabetes became more focused after type 1 and 2 diabetes could be differentiated as separate disease entities in the early 1970s (26). One of the first notions that there was a putative effect of nutritional factors was after the observation of an accelerated weight gain during infancy in children who later developed type 1 diabetes compared with control children (27). A timeline of studies that showed a possible relation between nutritional factors and the development of type 1 diabetes is provided in **Figure 1**. So far, the evidence in this field is fragmentary because very little systematic research has been conducted.

Most of the research on nutrition in the etiology of type 1 diabetes has been based on animal studies or ecologic comparisons, ie, studies that are useful in generating hypotheses but not in testing them. Case-control, cohort, and human-intervention studies—which can be used for hypothesis testing—are few in this research field, and only some of the findings have been replicated (**Table 1**). Infant feeding has been studied extensively in a series of case-control studies, although the results remain inconclusive. So far, only 4 case-control studies with clinical type 1 diabetes as an endpoint have evaluated some aspects of childhood diets at one point in time (**Table 2**). Studies have focused on single dietary factors, and, accordingly, the total diet of the child has not been assessed in relation to the risk of type 1 diabetes. Results of longitudinal assessments of nutrition are forthcoming. Preliminary findings about infant feeding from first-birth cohort studies on the natural development of β cell autoimmunity have been published (**Table 3**). In addition, nutritional findings are available from one point in time from a sibling cohort of subjects with type 1 diabetes (80, 83) and from some population-based cohorts (58, 94). Randomized clinical trials, which provide the strongest evidence for a causal relation, have been completed only with pharmacologic doses of nicotinamide (93, 108). The first nutritional primary prevention trial to compare weaning with either a hydrolyzed casein formula or with a regular cow milk–based infant formula was initiated in 2002 (109).

MAIN NUTRITIONAL CONSTITUENTS UNDER INVESTIGATION AND THEIR PUTATIVE MECHANISMS OF ACTION

The mechanisms of action of different nutritional constituents that may play a role in the development of β cell autoimmunity are largely unknown. It also remains to be defined whether these exposures or lack thereof initiate β cell autoimmunity or promote or accelerate an ongoing process. The effects of nutritional risk predictors may be different in the fetal period, in early infancy, and later in childhood. The effects may be specific or nonspecific, eg, a dietary protein might induce immunity cross-reacting with a specific β cell antigen, or obesity could modify the natural course of β cell autoimmunity through general effects on the immune system. Individual characteristics such as the *HLA* genotype most probably modify the effects of environmental factors.

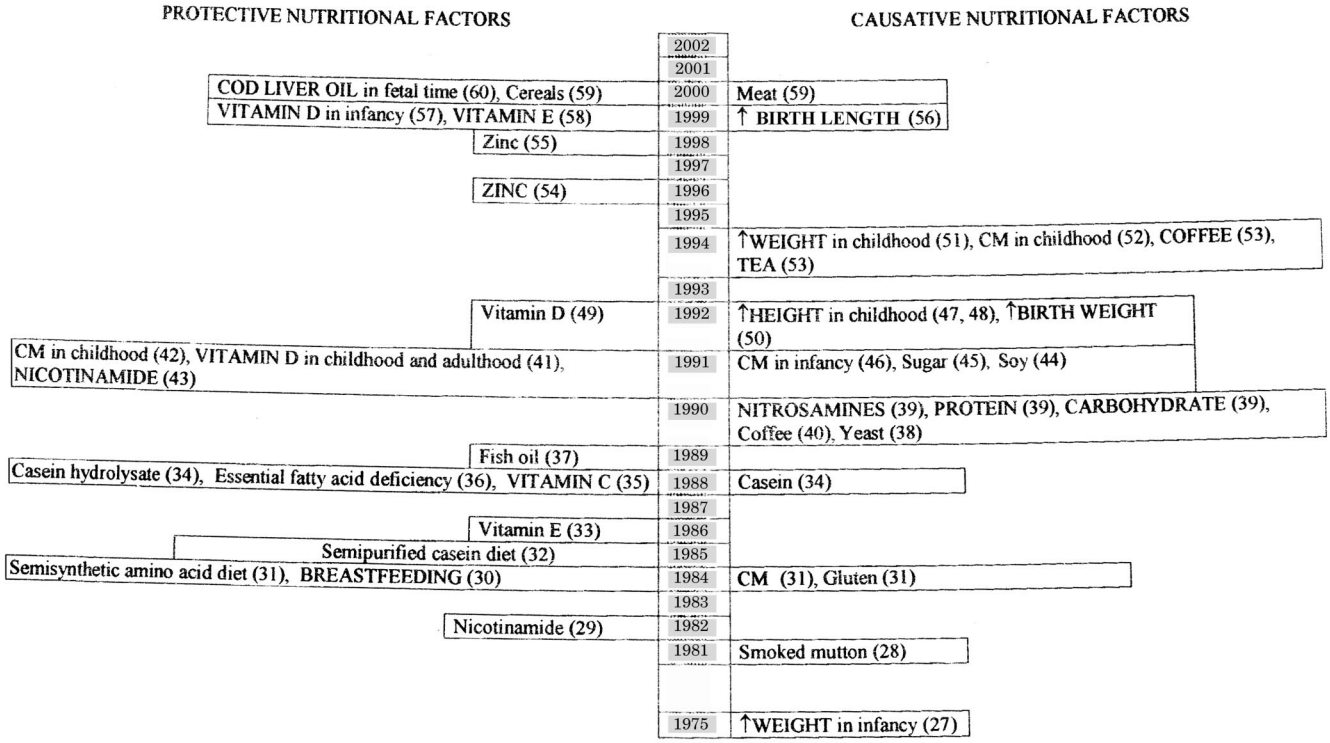

FIGURE 1. Time points when possible associations between different nutritional factors and the development of type 1 diabetes were first reported according to ecologic, animal, and human case-control, cohort, and intervention studies. The human studies are indicated by the use of all uppercase letters. CM, cow milk; ↑, increase.

The observation from the early 1970s about the association of increased weight gain in infancy with greater risk of type 1 diabetes has been confirmed and broadened later to possibly comprise increased height and weight gains during childhood as risk predictors (Table 1). Accelerated weight gain with greater intakes of energy has been observed in formula-fed compared with breastfed infants from 3 mo of age (110). By increasing insulin demand, increased weight gain induced by supplementary feeding could be a contributing factor in the development of type 1 diabetes. However, according to the

TABLE 1
Nutritional factors in the etiology of type 1 diabetes according to published studies in humans[1]

	Case-control studies			Cohort studies				
Exposure period	Fetal time	Infancy	Childhood/ adulthood	Fetal time	Infancy	Childhood/ adulthood	Clinical trials	Reference
Breastfeeding		**−/0/+**[2]			0/+			30, 35, 42, 46, 52, 61–85
Cow milk		**0/+**	0/+		0	+		39, 46, 52, 61, 68, 70, 72, 73, 75–77, 80, 82–91
Coffee, tea	0		+					53, 61
Cod liver oil	−	0						60
Nitrate, nitrite, or *N*-nitroso compounds	+		0/+					39, 52, 67, 92
Nicotinamide							−/0	43, 93
Vitamin C			−/0					35, 39
Vitamin D		−/0	−		−			41, 57, 60, 94
Vitamin E						−		58
Zinc			−					54
Weight gain	**0/+**[3]	**+**	**0/+**	+				27, 47, 50, 51, 56, 61, 77, 78, 85, 90, 95–102
Height gain	**0/+**[3]	0/+	**+**					47, 48, 56, 61, 66, 85, 96, 97, 99–101
Maternal weight gain during pregnancy	0/+							95, 103

[1] Updated from reference 11. Only studies with clinical type 1 diabetes as an endpoint were included: minus signs refer to a significant, inverse, protective association; the zeros represent no association; and the plus signs indicate a significant positive, causative association.

[2] Findings from ≥ 3 studies are in boldface.

[3] Measurements were made at birth.

TABLE 2
Case-control studies of childhood diet and development of type 1 diabetes[1]

Country and reference	Time period of interest	Selection of controls	Diet assessment	Dietary variables analyzed	Confounders in analysis	Direction of association between diet and type 1 diabetes[2]
Canada, 1983–1986 (67) Cases (n = 161) Controls (n = 321)	Before symptoms of diabetes	Sex, age-matched from neighborhood	Use of 6 foods with high content of *N*-nitroso compounds (≥weekly compared with less)	Bacon, bologna, salami, sausages, pepperoni, smoked meat	—	None
Sweden, 1985–1986 (39, 42) Cases (n = 339) Controls (n = 528)	Food habits before recent change (3 mo)	Age, sex, county-matched, population-based	Weekly frequency of use of 36 foods	Protein, fat, carbohydrate[3], mono- and disaccharides, nitrosamines, nitrates or nitrites, fiber, vitamin C, CM, CM products	Age, sex, maternal age, education, type 1 diabetes in family	Protein (+), carbohydrate (+), nitrosamines(+), CM (−)
Australia, 1990–1991 (52) Cases (n = 217) Controls (n = 258)	1-y time period before symptoms of diabetes	Age, sex-matched, population-based	Semiquantitative FFQ focusing on CM and cereal protein, foods likely to contain nitrosamines, fluids[4]	CM and cereal protein, nitrosamine-containing foods	Fluid intake	CM protein (+)
Finland (53, 88, 92) Cases, 1986–1989 (n = 746) Controls, 1988–1990 (n = 690)	Before symptoms of diabetes	Birth date, sex-matched, population-based	Amount of coffee, tea, CM, and sour CM used daily, FFQ of foods providing ≥3% of nitrate or nitrite, nitrate, nitrite from tap water	CM and sour CM[5], coffee, tea use, nitrate and nitrite intake from food and drinking water	Age, sex, area of residence, maternal age, education	Nitrite (+), tea (+), coffee (+)

[1] Only studies with clinical type 1 diabetes as an endpoint were included. CM, cow milk; FFQ, food-frequency questionnaire.
[2] Plus signs indicate a positive association; minus sign indicates a negative association.
[3] Only solid foods high in protein, fat, and carbohydrate were considered.
[4] Individual foods were not specified.
[5] Comparisons of CM and sour CM consumption were restricted to those 86 case-control pairs who were studied at the same time, because of changes in consumption during the study (88).

case-control findings, rapid weight gain in infancy and early exposure to cow milk are both independent risk predictors of type 1 diabetes (90). It has been proposed that either genetically determined rapid growth, which increases the exogenous insulin demand, or a genetic tendency to hyperinsulinemia, which leads to accelerated growth, could explain why enhancements in height have been observed to be associated with an increased risk of type 1 diabetes (47). Hyperinsulinemia can also be induced by overweight. Obese children grow faster than do other children (111). Hyperfunctioning β cells are more susceptible to cytokine-induced toxicity (112), and increased insulin secretion may stimulate antigen presentation by β cells (113).

Breastfeeding may protect against type 1 diabetes (Table 1). The putative mechanisms of action include protection against infections provided by breast milk through, for example, secretory immunoglobulin A (IgA) antibodies and enhancement of the infant's own immune responses; increased β cell proliferation, which has been observed in breastfed compared with formula-fed infants (114); or delayed exposure to foreign food antigens. Breast milk contains many cytokines and growth factors, which affect the maturation of the gut-associated lymphoid tissue (GALT) (115). Maternal diet and composition of breast milk may play a role in the development of immune-mediated diseases. Breast milk also contains high concentrations of human insulin (116), a potentially crucial antigen in the process leading to type 1 diabetes. Such an exposure could induce regulatory cells, which facilitates tolerance development. It is, however, unlikely that this would play a significant protective role in relation to type 1 diabetes, because the fetus experiences mucosal exposure to human insulin via the continuous ingestion of amniotic fluid, which contains measurable concentrations of insulin (117). It has been shown that small amounts of cow milk proteins may be carried over to breast milk from the maternal diet. A low concentration of β-lactoglobulin, a cow milk–specific protein, has been detected in breast milk (118), and very sensitive infants may develop an allergy to cow milk if exclusively breastfed (119). This raises the issue of the possible transfer of bovine insulin through breast milk in breastfed infants. There is a structural difference of 3 amino acids between porcine and human insulin, and it has been shown that bovine insulin in cow milk–based formulas induces initially an immune response to bovine insulin (120).

TABLE 3
Relation of the duration of breastfeeding and the age at introduction of cow milk (CM) to the appearance of type 1 diabetes–associated autoantibodies according to available birth-cohort studies[1]

Study and reference	Endpoint: positivity for	No. of seroconverters/total	EB/TB	Association between breastfeeding and seroconversion, risk ratio (95% CI)	Age at introduction of CM	Association between age at introduction of CM and seroconversion, risk ratio (95% CI)
DAISY (104)[2]	At least one of IAA, GADA, IA-2A	18/171	Ever breastfed	OR = 1.3 (0.3, 6.0)	Before 3 or 6 mo of age	OR = 0.4 (0.1, 1.2) OR = 0.5 (0.2, 1.4)
German BABY-DIAB (105)[3]	One of IAA, GADA, IA-2A, ICA	31/823	EB > 3 mo	RR = 1.3 (0.5, 3.0)[4] RR = 0.7 (0.2, 2.5)[5]	—	—
			TB > 3 mo	RR = 1.5 (0.6, 3.3)[4] RR = 0.7 (0.2, 2.2)[5]		
Australian BABY-DIAB (106)[6]	One of IAA, GADA, IA-2A	52/317	EB, continuous TB, continuous	HR = 1.0 HR = 1.0	CM-based infant formulas, continuous	HR = 1.0
	One repeatedly	18	EB, continuous TB, continuous	HR = 1.0 HR = 1.0	CM-based infant formulas, continuous	HR = 1.0
	At least 2	22	EB, continuous TB, continuous	HR = 1.0 HR = 1.0	CM-based infant formulas, continuous	HR = 1.0
DIPP (107)[7]	IAA	41/455	EB: 2–3.9 vs < 2 mo ≥ 4 vs < 2 mo	OR = 1.1 (0.5, 2.4) OR = 0.7 (0.3, 1.7)	CM: < 2 vs ≥ 4 mo 2–3.9 vs ≥ 4 mo	OR = 1.4 (0.6, 3.0) OR = 2.0 (0.7, 5.8)
	GADA	32	EB: 2–3.9 vs < 2 mo ≥ 4 vs < 2 mo	OR = 1.2 (0.5, 3.0) OR = 0.7 (0.3, 1.9)	CM: <2 vs ≥ 4 mo 2–3.9 vs ≥ 4 mo	OR = 1.3 (0.6, 3.1) OR = 1.5 (0.4, 5.1)
	IA-2A	24	EB: 2–3.9 vs < 2 mo ≥ 4 vs < 2 mo	OR = 0.8 (0.3, 2.4) OR = 0.2 (0.1, 0.9)[8]	CM: < 2 vs ≥ 4 mo 2–3.9 vs ≥ 4 mo	OR = 4.4 (1.3, 14)[8] OR = 5.5 (1.2, 25)[8]
	ICA	65	EB: 2–3.9 vs < 2 mo ≥ 4 vs < 2 mo	OR = 1.1 (0.6, 2.1) OR = 0.9 (0.5, 1.7)	CM: < 2 vs ≥ 4 mo 2–3.9 vs ≥ 4 mo	OR = 1.1 (0.6, 1.9) OR = 1.3 (0.6, 2.9)
	One of 4	22	EB: 2–3.9 vs < 2 mo ≥ 4 vs < 2 mo	OR = 1.5 (0.5, 4.5) OR = 1.2 (0.5, 3.5)	CM: < 2 vs ≥ 4 mo 2–3.9 vs ≥ 4 mo	OR = 0.6 (0.2, 1.6) OR = 0.7 (0.2, 2.9)
	Two or 3 of 4	24	EB: 2–3.9 vs < 2 mo ≥ 4 vs < 2 mo	OR = 1.1 (0.4, 3.2) OR = 1.7 (0.6, 4.8)	CM: < 2 vs ≥ 4 mo 2–3.9 vs ≥ 4 mo	OR = 0.7 (0.3, 1.7) OR = 0.8 (0.2, 3.1)
	All 4	19	EB: 2–3.9 vs < 2 mo ≥ 4 vs < 2 mo	OR = 0.8 (0.2, 2.8) OR = 0.2 (0.03, 0.9)[8]	CM: < 2 vs ≥ 4 mo 2–3.9 vs ≥ 4 mo	OR = 5.0 (1.3, 20)[8] OR = 6.2 (1.1, 35)[8]

[1] EB, exclusive breastfeeding; TB, total breastfeeding; OR, odds ratio; RR, risk ratio; HR, hazard ratio; IAA, insulin autoantibodies; IA-2A, insulinoma-associated protein-2 antibodies; ICA, islet cell antibodies; GADA, glutamic acid decarboxylase antibodies.

[2] Cross-sectional part of the Diabetes Autoimmunity Study in the Young, which involved the study of first-degree relatives (aged < 7 y) of subjects with type 1 diabetes.

[3] Newborn offspring of parents with type 1 diabetes followed up to the age of 2 y.

[4] Mother with type 1 diabetes.

[5] Father with type 1 diabetes.

[6] Newborns with first-degree relative with type 1 diabetes observed for a median of 29 mo.

[7] β Cell autoimmunity cases and their sex-, birth date–, *HLA-DQB1* genotype–, and area-matched control subjects selected from a population-based cohort of 2949 newborns with an increased genetic risk of type 1 diabetes; median follow-up time of 2.5 y. Adjusted for maternal age, education, and child's relative height and weight at the age of 1 y in the analysis.

[8] $P < 0.05$.

Several theories have been proposed to explain the putative diabetogenicity of cow milk (10). Whether early immunization to bovine insulin is related to the development of β cell autoimmunity remains to be confirmed. A lack of normal tolerance development has been observed in infants who develop early signs of β cell autoimmunity (120). This raises the possibility that the initial immune response to bovine insulin may, in some persons, be diverted into an autoimmune response that targets human insulin and the insulin-producing β cell (121). The putative diabetes-promoting effects of cow milk and other dietary antigens may be mediated through GALT (*see* below: Nutrition, microbes, and autoimmunity). Whether changes in gut permeability caused by microbial infections enable food proteins to induce β cell autoimmunity remains to be defined.

Several *N*-nitroso compounds, such as streptozotocin, have well-known toxic effects on pancreatic β cells in animals (122). The mechanisms of action of various diabetogenic *N*-nitroso compounds are different in terms of their capability of damaging cell organelles through the generation of free oxygen radicals or via the induction of DNA strand breaks. In some cases, diabetes may even be transferred to successive generations of rats (123, 124).

Some vitamins and minerals have been proposed to protect against type 1 diabetes. The putative protective effects of vitamin D may be related to the induction of regulatory cytokines, resulting in the induction of regulatory cells with the capability of down-regulating autoaggressive immune responses. Vitamin D administration has been shown to increase interleukin 4 (IL-4) and transforming growth factor β messen-

ger RNA and to decrease concentrations of interferon γ and tumor necrosis factor α messenger RNA. This implies that vitamin D may specifically induce a deviation in the immune system, specifically a deviation in T helper cells subset 2 (125, 126). The biological effects of vitamin D are likely influenced by polymorphisms with the vitamin D–receptor gene (127). Little is known about the immunologic effects of vitamin D in humans, however. Vitamin E could prevent type 1 diabetes through its function as an important free radical scavenger (128) as well as through the inhibition of *N*-nitroso compound formation in food and in the human organism (129).

ANIMAL AND ECOLOGIC FINDINGS

Diabetes-prone Bio Breeding (BB) rats, nonobese diabetic (NOD) mice, and low-dose streptozotocin-induced diabetic mice are the most studied animal models of immune-mediated diabetes. Several animal and vegetable proteins have been shown to induce diabetes in these animals and some vitamins and minerals to protect against disease. However, the evidence is inconclusive both within and between these animal models. For example, the diabetogenicity of cow milk is different in BB rats and NOD mice (130). One may also ask how relevant observations made in studies performed in these animal models may be in the context of human type 1 diabetes. Bafilomycin A1, which is produced by *Streptomyces* species in soil, was recently shown to induce glucose intolerance and to reduce pancreatic islet size in mice (131). *Streptomyces* species can infest tuberous vegetables such as potatoes and beet.

Cow milk, coffee, sugar, and meat products have been positively and cereal products inversely related to the risk of type 1 diabetes in ecologic correlation studies that compared per capita consumption with disease incidence (40, 45, 59, 132, 133). An inverse correlation was observed between the frequency of breastfed children at the age of 3 mo and the incidence of type 1 diabetes in several countries (132), whereas breastfeeding frequency during the past 20 y was not related to the incidence of diabetes in Sweden (134). Nitrate concentrations in drinking water correlated weakly with the incidence of type 1 diabetes in some populations (135, 136) but not in others (137, 138). Compared with the rest of the country, a lower incidence of type 1 diabetes was found in coastal districts in Norway, where fishing is actively performed (139). The number of sunshine hours was inversely related to the incidence of type 1 diabetes in Swedish counties (140).

RISK PREDICTORS DURING FETAL LIFE

The evidence that type 1 diabetes–associated autoantibodies may start to emerge early in infancy (16, 17), and that maternal enterovirus infections during pregnancy may increase the risk of progression to clinical type 1 diabetes in the offspring (141), emphasizes the importance of studying prenatal risk predictors. The transfer of nutrients to the fetus depends on maternal status and on the adequacy of uterine blood flow. Fat-soluble vitamins cross by simple diffusion, carbohydrates by facilitated diffusion, and amino acids, water-soluble vitamins, and some minerals by active transport (142). There is also transfer of anti-idiotypic antibodies from the mother to the fetus (143), eg, IgG antibodies to cow milk are present in umbilical serum (144).

Evidence indicates that the intrauterine environment can affect the risk of developing type 1 diabetes. Preeclampsia, excessive weight gain, amniocentesis, maternal-child blood group incompatibility, maternal enterovirus infections, and prenatal growth are related—although not consistently so—to the risk of type 1 diabetes (56, 95, 98, 103, 141). Some of these factors may have links to the diet (145).

Most case-control studies report similar weights at birth in infants who later develop type 1 diabetes and in control infants (27, 47, 61, 77, 78, 95, 96, 99, 100) or nondiabetic siblings (96, 101). In 3 studies, the birth weight was higher in those who developed diabetes (50, 85, 102), and in one study this difference was seen only in boys (101). In a pooled case-control analysis from several European countries, low birth weight and short birth length were related to a decreased risk of type 1 diabetes (56). Also, in another series, short birth length was associated with a decreased risk of diabetes (85, 101). In most surveys, similar birth lengths were observed in children who later developed diabetes and in population-based (61, 66, 96, 99, 100) or sibling (96, 101) control groups. Ponderal index at birth did not differ between cases and control subjects (101). A large nested case-control comparison between $\approx$4500 children with diabetes and control subjects matched for year of birth showed that low birth weight for gestational age was associated with a reduced risk of diabetes and high birth weight with an increased risk (98).

Maternal coffee or tea consumption during pregnancy was not related to the risk of type 1 diabetes in the offspring in Hungarian and Finnish case-control series (53, 61). Maternal nitrite intake was positively associated with the risk of diabetes independently of the child's own intake and when adjusted for several sociodemographic factors (92). The father's use of coffee or tea or intake of nitrate or nitrite at the time of conception was unrelated to the risk of diabetes in the offspring (53, 92). In the Finnish study, parental age and education, smoking, and area of residence were taken into account as potential confounders. Norwegian case-control findings of an inverse association between maternal cod liver oil supplementation during pregnancy and the risk of type 1 diabetes in the offspring suggest that either vitamin D, vitamin A, or n$-$3 fatty acids, which are all abundant in cod liver oil, play a role in the development of this disease (60). The status of these fat-soluble vitamins as well as that of eicosapentaenoic acid and docosahexaenoic acid (146) in newborns reflects that of his or her mother. Eicosapentaenoic acid and docosahexaenoic acid have antiinflammatory properties, because they decrease the production of IL-1, IL-2, IL-6, tumor necrosis factor α, and interferon γ in human mononuclear cells (147). These fatty acids also decrease the expression of HLA class II molecules and ICAM-1 on activated human monocytes (147). All polyunsaturated fatty acids seem to inhibit production of T helper cell subset 1–type cytokines, with little effect on T helper cells subset 2–type cytokines, although n$-$3 fatty acids are particularly potent in this respect (148).

INFANCY

Breastfeeding and complementary feeding

Some case-control studies suggest that breastfeeding protects against type 1 diabetes, whereas in others no association

was observed (Table 1). Several case-control findings point to the putative diabetogenicity of an early introduction of supplementary milk feeding. Altogether there are somewhat more cases in studies that have reported an inverse association between age at introduction of supplementary milk and the risk of type 1 diabetes compared with studies without any association ($n = 1612$ compared with 1061). The large size of the Finnish nationwide case-control study population enabled a comparison of the duration of breastfeeding and age at introduction of supplementary milk, which suggested that the causative effects of early introduction of cow milk may overcome the protective effects of breastfeeding (72). The statistical power of the available cohort study of initially nondiabetic siblings of children with diabetes (83) was too weak to detect a relative risk of the same magnitude as that observed in several case-control studies. Four birth cohort studies reported preliminary findings on the relation between infant feeding patterns and the emergence of type 1 diabetes–associated autoantibodies (Table 3). The number of seroconverters in all of these studies was small, and, accordingly, the statistical power was low. The findings of these studies are consistent in showing no association of breastfeeding or age at introduction of supplementary milk feeding with emergence of up to 3 autoantibodies. However, only in the Finnish type 1 DIPP Study was the relation of infant feeding to the outcome of having all 4 predictive autoantibody specificities positive at the same time evaluated (Table 3). Also, only in the DIPP Study was the emergence of IA-2A specifically used as an outcome. Short-term exclusive breastfeeding and the early introduction of supplementary milk feeding were related to an increased risk of developing all 4 autoantibodies and IA-2A (Table 3). Only in the DIPP Study were the control subjects matched for the *HLA-DQB1* genotype and putative sociodemographic confounders taken into account. In the pilot study of the Trial to Reduce IDDM in the Genetically at Risk, feeding with a highly hydrolyzed infant formula resulted in a decreased cumulative incidence of type 1 diabetes–associated autoantibodies by the age of 2 y compared with weaning to a regular cow milk–based formula (109). On the basis of the findings of animal studies, food proteins other than those in cow milk might be diabetogenic. In humans, hardly any evidence exists on the relation between age at introduction of food proteins other than milk and the development of type 1 diabetes. In a series of 18 cases that were positive for ≥ 1 of 3 autoantibodies, no differences were observed between cases and control subjects in the age at introduction of cow milk, cereal, fruit and vegetables, or meat protein (104). A later preliminary report from the same Colorado study suggests that both the early (before the age of 4 mo) and late (after the age of 6 mo) introduction of cereal proteins may be associated with an increased risk of β cell autoimmunity compared with the introduction between the ages of 4 and 6 mo (149).

Vitamin D

The active form of vitamin D (1,25-dihydroxyvitamin D) prevents autoimmune diseases such as multiple sclerosis, arthritis, and diabetes in several animal models of human disease (126). In NOD mice and low-dose streptozotocin mice, insulitis and diabetes were prevented by long-term intraperitoneal treatment with high doses of active vitamin D_3 (150, 151) or its analogue (49). Recently, short-term oral treatment with a vitamin D analogue at a nonhypercalcemic dose was shown to effectively prevent diabetes in NOD mice (125). Genetic polymorphism in the vitamin D receptor locus or nearby has been suggested to be linked to type 1 diabetes (eg 127) and to be a genetic regulator of early postnatal growth (152, 153).

Vitamin D supplementation during infancy was inversely associated with the risk of type 1 diabetes in a European case-control comparison (57), whereas vitamin D or cod liver oil use during infancy was not related to the risk of diabetes in a small Norwegian case-control series (60). In a Finnish birth cohort study, the use of vitamin D supplements during infancy and the supplementation dose were both inversely related and the suspicion of rickets was directly related to the risk of developing type 1 diabetes (94). In 1966, at the time of birth of the study subjects, the recommended daily dose of vitamin D supplementation was 2000 IU in Finland, ie, 5 times the current recommendation.

Growth

Increased weight gain in infancy has been consistently associated with an enhanced risk of type 1 diabetes in case-control studies (27, 51, 85, 90, 96). Height was positively related to the risk of type 1 diabetes in 2 studies (85, 97) but not in one study (96).

CHILDHOOD

Only 4 case-control studies have provided evidence for a relation between diet after infancy and the development of type 1 diabetes (Table 2). Regarding the selection of cases, all of the studies were population-based and the same was true for the controls except in one survey. All of the studies focused on the diet before symptoms of diabetes occurred. However, only some aspects of the children's diet, not the total diet, were evaluated at one point of time.

Cow milk

Increased numbers of antibodies toward a series of cow milk proteins have been detected repeatedly in children with newly diagnosed type 1 diabetes (154). Increased concentrations of IgA-class β-lactoglobulin (86) and IgA cow milk formula antibodies (88) were related to an increased risk of type 1 diabetes. Both infant feeding patterns (86, 88) and current milk consumption (88) affect cow milk antibody titers. The case-control findings on the association between milk consumption during childhood and risk of type 1 diabetes are inconsistent. In an Australian study, a positive association was observed (52), whereas an inverse association was seen in Swedish children and no association was seen in young Finnish children (39, 88) (Table 2). A follow-up of initially nondiabetic siblings of children with type 1 diabetes showed that a higher milk consumption is associated with a greater risk of developing type 1 diabetes during the 10-year follow-up period (80, 83). The daily consumption of ≥ 0.5 L milk was associated with a 3-fold risk of diabetes, and the risk increased to 5 when the child's genotype was taken into account. This finding suggests an interaction between milk consumption and genetic risk (83).

Cereals

Animal studies have linked wheat gluten with an increased risk of autoimmune diabetes (31, 130). Higher concentrations

of antigliadin IgG antibodies were observed in Italian children with diabetes than in control children (155). No difference was seen in IgG-class gliadin antibodies in a Finnish study, whereas the IgA-class antibody concentrations were reduced (154). A greater reactivity of T cells to gluten was detected among children with newly diagnosed type 1 diabetes than in control children (156). In an ecologic comparison, per capita intake of cereal products was inversely related to the incidence of type 1 diabetes (59), whereas no relation was observed between cereal protein intake and the risk of diabetes in an Australian case-control study (52).

Coffee and tea

In our Finnish case-control study, an enhanced risk of type 1 diabetes was seen in the children who consumed coffee or tea daily, independently of putative confounding sociodemographic factors (53). In that study the families were asked to describe the children's food habits before any symptoms of diabetes appeared.

Energy and energy-yielding nutrients

A high consumption frequency of solid foods rich in protein and carbohydrate was related to an increased risk of type 1 diabetes in a Swedish case-control study (39, 42). The interpretation of these findings is hampered by the study design: only 36 food items were included, and total energy intake was not assessed. The results may simply reflect a higher intake of energy in cases than in controls, which suggests that either an increased energy intake could be a risk predictor of type 1 diabetes or that a higher intake of energy could be due to metabolic dysregulation induced by the diabetic state. The families of both the cases and the controls received the questionnaire by mail $\approx$4 wk after the diagnosis of diabetes. If the child had changed his or her food habits during the preceding 3 mo, the family was asked to describe the children's food habits before that change. This can be expected to decrease the possible effect of the diabetic state on the findings.

N-Nitroso compounds, nitrate, and nitrite

Ecologic, animal, and human case-control studies have implicated that dietary *N*-nitroso compounds, nitrate, nitrite, or a combination thereof may play a role in the etiology of type 1 diabetes (28, 39, 92). The most important exogenous source of *N*-nitroso compounds is food. In addition, they may originate from cigarettes, car interiors, and cosmetics. Processed meat and fish products and beer are the most important food sources. Nitrate and nitrite are used as food additives in the processing of meat products because of their antimicrobial action and their ability to improve color and taste. Nitrate and nitrite can also be found in food as naturally occurring compounds. Among Finnish children and adolescents, the most important sources of nitrate were potatoes, cabbages, carrots, and beet roots, whereas sausages provided most of the nitrite (157). It is noteworthy that the highest intakes of both nitrate and nitrite in relation to body weight were observed in the youngest children (157). In food and in the gastrointestinal tract, nitrate can be reduced to nitrite, which may react with certain amines and amides leading to the formation of toxic *N*-nitroso compounds. This reaction is inhibited by α-tocopherol and vitamin C and is accelerated by thiocyanate (129, 158).

Four case-control studies have assessed the significance of dietary *N*-nitroso compounds, nitrate, nitrite, or a combination thereof in the development of type 1 diabetes (Table 2). The Canadian study compared the consumption frequencies of 6 meat products high in nitrosamines, but did not find a difference between cases with diabetes and controls (67). The Swedish study reported that the frequency of the use of foods containing nitrosamines (eg, smoked fish, bacon, and smoked sausage) in the highest quartile compared with lowest quartile was associated with a 2.5-fold risk of diabetes (39). This risk ratio remained significant when protein intake from solid foods was taken into account. In the Australian study, those children who consumed higher amounts of foods that were likely to contain nitrosamines did not have an increased risk of diabetes (52). Food items rich in nitrosamines were not defined in that report. In our Finnish case-control study, we asked for the consumption frequencies of foods that provided $\geq$ 3% of the total intake of nitrate and nitrite, respectively (157). The children's nitrate intake was not related to the risk of diabetes, whereas the children's nitrite intake in the highest quartile was associated with a 2.4-fold risk of diabetes compared with the lowest quartile, and among children aged $<$ 7 y this risk ratio was 4.5 (92). The case and control children had similar intakes of nitrate and nitrite from drinking water in that study. Note that the concentration of nitrate and nitrite in Finnish water is low on average, whereas nitrate and nitrite concentrations were not available from private well waters, which may contain higher concentrations. In the Swedish and Finnish studies, several putative confounding sociodemographic factors were taken into account in the analysis (Table 2). Animal data suggest that nitrosamines increase the diabetogenic effect of certain viruses (159).

Vitamins and minerals

Lower serum concentrations of active vitamin D (1,25-dihydroxy D_3) were observed in adolescents and adults with newly diagnosed type 1 diabetes than in controls of a similar age (41). In a nested case-control study within an adult Finnish cohort, an inverse relation was observed between serum concentrations of α-tocopherol at baseline and the development of type 1 diabetes 4–14 y later (58). The association was independent of serum cholesterol concentrations and body mass index. Serum selenium or retinol concentrations were not related to the risk of type 1 diabetes in that study. In a small Finnish cross-sectional series of healthy children, no difference in plasma α-tocopherol, ascorbic acid, or total plasma antioxidant activity was seen between children positive for type 1 diabetes–associated autoantibodies and autoantibody-negative subjects (160). An Australian case-control study reported that vitamin C supplementation was inversely related to the risk of type 1 diabetes (35). Zinc concentrations in drinking water were also observed to be inversely related to the risk of type 1 diabetes in a Swedish case-control study (54).

Some of the randomized placebo-controlled trials in subjects with recently diagnosed type 1 diabetes suggest that nicotinamide delays the decay of β cell function, whereas in others no effect was observed (161). Two small open trials in high-risk persons with increased ICA titers and decreased first-phase insulin release observed positive effects of nicotinamide (43, 162). A German and an international double-blind randomized

clinical trial failed to show any effect of nicotinamide on the progression to clinical diabetes in young first-degree relatives with elevated ICA concentrations (93; EAM Gale, personal communication, 2002).

Increased weight and height gain

Weight gain during childhood was unrelated to the risk of type 1 diabetes both in Swedish (47) and Dutch (96) case-control series. A positive relation was observed among Finnish children, in the EURODIAB study (85, 97), and among Swedish children younger than 2.5 y of age (51). Increased height gain has been consistently related to an increased risk of diabetes (47, 48, 85, 96, 97). In the Dutch study (96), both children with diabetes and their siblings were taller than the population controls. Parental heights of cases and controls have been observed to be similar in children with type 1 diabetes and their controls (96, 97).

All studies that have evaluated the associations between growth and the risk of type 1 diabetes have been case-control studies. Most of them were based on growth records completed at the time of measurement, which minimized the possibility of information bias. However, some degree of selection bias is likely in all of the studies because of the lower participation rates among control than among case subjects. Clearly, evidence from cohort studies is needed before any firm conclusions can be drawn. Most studies reported in this field thus far have not taken advantage of the longitudinal nature of the growth data in the statistical analysis, although comparisons of single time points only can be misleading.

Obesity is inversely associated with the status of vitamin E and several other antioxidants (163, 164). Whether the relation between vitamin E status and the risk of type 1 diabetes is at least partly explained by obesity or vice versa needs to be clarified.

NUTRITION, MICROBES, AND AUTOIMMUNITY

Cesarean delivery (95, 103) and decreased exposure to common infections during infancy (165) have been linked to an increased risk of type 1 diabetes; higher birth order (77, 166, 167) and daycare attendance (168, 169) have been linked to a reduced risk, although the findings remain inconsistent (56, 79). These associations give a hint that decreased or changed exposure to microbes may be involved in the development of type 1 diabetes. Some dietary components may have an effect on gut microbes and GALT (170).

There is increasing evidence both in humans and rodents that GALT, which is the most extensive immune organ in the organism, is involved in the development of type 1 diabetes, most likely through abnormal oral tolerance mechanisms (171). The possibility of dietary regulation of autoimmunity through GALT has been raised (172). Scott et al (173) reported recently that oral exposure to diabetes-promoting food antigens and immune modulators in neonatal BB rats can affect the local cytokine balance in the gut and is accompanied by an increased rate of diabetes. The neonatal period is particularly critical in terms of the induction of oral tolerance. The intestinal barrier function and the immunoregulatory network are poorly developed for a variable period of time after birth (170). The postnatal development of mucosal immune homeostasis is related to the establishment of a normal commensal microbial flora and on adequate timing and dose of food antigens when first introduced. Breastfeeding appears to facilitate the development of normal oral tolerance.

Certain enterovirus or rotavirus infections during fetal time or in infancy may be associated with β cell autoimmunity and the development of clinical type 1 diabetes (141, 174, 175). Enteral infections may increase the transfer of foreign antigens through the gut mucosa and thereby prime GALT to sensitization to dietary components. Novel data from the Finnish DIPP study indicate that early enterovirus infections enhance the sensitization to bovine insulin in formula-fed infants, which suggests, accordingly, an interaction between 2 environmental risk factors for type 1 diabetes (176). Evidence exists that breastfeeding may protect against enterovirus infections and other enteric infections (177), which may contribute to the implicated protective effect of breastfeeding against type 1 diabetes.

COMMON RISK PREDICTORS OF TYPE 1 AND TYPE 2 DIABETES

Although subjects who later develop type 2 diabetes are thinner at the time of birth (178), those who develop type 1 diabetes do not seem to differ from others in this respect or may even weigh more in relation to gestational age (98). However, short-term exclusive breastfeeding and an early age at introduction of supplementary feeding have been suggested as risk predictors of both type 1 and type 2 diabetes (179). Increased weight gain may be an important accelerator of not only type 2 diabetes, but also of type 1 diabetes (51, 85, 97, 180). An association has also been observed between increased body mass index and the presence of glutamate decarboxylase antibodies in unaffected male first-degree relatives of subjects with type 1 diabetes (181) and among glucose-intolerant men and women (182). Weight gain has been suggested to be the missing link between type 1 and type 2 diabetes (180), which could be the same disease, distinguishable only by their rate of β cell loss and responsible accelerators (intrinsically high rate of β cell apoptosis, insulin resistance, and autoimmunity).

Several studies have suggested that type 1 and type 2 diabetes overlap within families (183, 184). Recent findings from a population-based prospective family study suggest, however, that there is no excess of nonautoimmune diabetes among the parents of children with type 1 diabetes (185). This latter study differs from previous ones in that the discrimination between type 1 and type 2 diabetes was based not only on clinical features but also on the analysis of type 1 diabetes–associated autoantibodies. However, the target group did not include grandparents, and the number of cases was moderate. Accordingly, this observation awaits confirmation by other studies.

OTHER IMMUNOLOGIC OR AUTOIMMUNE DISEASES AND TYPE 1 DIABETES

Celiac disease coexists with type 1 diabetes, the prevalence ranging from 2% to 8.5% among children with diabetes (186). In addition to the known common genetic risk predictor, ie the *HLA DR-DQ2* haplotype, this coexistence may implicate that one of the diseases is a pathogenic consequence of the other. Recently, type 1 diabetes–associated autoantibodies were observed to be less frequent in those subjects with celiac disease

who consumed a gluten-free diet than in those who did not in a small series of adolescents with celiac disease (187).

Allergic diseases, asthma in particular, have become more common over the past decades in developed countries (188, 189). A recent ecologic comparison showed a strong positive correlation between the occurrence of type 1 diabetes and symptoms of asthma at the population level (190), thus suggesting that these 2 immune-mediated diseases may share risk predictors. At an individual level, an inverse relation has been suggested to exist between type 1 diabetes and allergic diseases. Children with type 1 diabetes have less asthma (191–193) and less atopic dermatitis (194) than do other children according to some case-control studies, although other case-control and cohort findings have shown no association between type 1 diabetes and asthma (195, 196) or atopic dermatitis (195). Reduced microbial exposure during the first years of life has been implicated as a factor contributing to the increasing prevalence of both type 1 diabetes and allergic diseases (197), the only common risk predictor of these diseases suggested so far being short-term breastfeeding or an early introduction of formula feeding (198).

METHODOLOGIC CONSIDERATIONS OF STUDYING DIET-DISEASE RELATIONS

Some special features of the diet complicate studies on diet-disease relations. Dietary intakes of many foods and nutrients are strongly related, and almost everyone is exposed to most of the dietary factors and diet includes several types of exposures: foods, nutrients, microbial toxins, chemicals formed during cooking, etc. Dietary factors may act as effect modifiers or confounders to each other and to other exposures. In dietary case-control studies, information and selection biases may lead to more serious problems than in other types of case-control studies. Because of moderate risk ratios usually observed in dietary studies, biases of the size typical to case-control studies might seriously distort the results (199). Different dietary variables can be measured with variable accuracy. Day-to-day variation is smaller for the intake of energy than of vitamin E, which means that we need a shorter time period to assess a person's energy intake than his or her intake of vitamin E with a given level of reliability.

Type 1 diabetes occurs at a relatively low frequency and is likely to be a multifactorial disease with a subclinical prodrome of variable duration. Presumably, exposures to putative causative or protective factors over several years are important, not just at one time point. This means that in the studies of the etiology of type 1 diabetes, large sample sizes are needed and the long-term diet is of interest. Traditional food consumption methods, such as food records or 24-h dietary recalls, need to be repeated to cover the day-to-day variation in dietary intakes as well as to give an estimate of the long-term diet and therefore require extensive resources. Food-frequency questionnaires have been developed and validated extensively but, unfortunately, mainly for adult populations (199). The development of good markers of preclinical type 1 diabetes and the identification of risk genotypes over past decades have, however, made the use of traditional food consumption methods feasible to be used, even in cohort settings.

To promote proper use of nutritional methods, the scientific journals should pay particular attention to the adequate description of dietary methods, even when traditional methods are used. It is important to know which food and nutrient databases are used, their quality, and the amount of food items and recipes included. The quality of the data are affected by how skillful and well trained the research personnel are and by how standardized the data collection and entering are. When new methods are developed, they should be validated.

LIFESTYLE CHANGES AND INCREASING INCIDENCE OF TYPE 1 DIABETES

Along with the steady increase in the incidence of type 1 diabetes in most developed countries after World War II, many changes have occurred in relation to nutrition. In industrialized countries the diet has become more processed and sterile, and the ratio of n−6 to n−3 fatty acids has increased. The exposure to microbes via foods and the consumption of foods that affect gut microbes has changed dramatically by the development of refrigeration, heating, and food-processing technologies. For example, the pasteurization of cow milk in Finland began in 1946 and homogenization in the 1960s. Such processing modifies the characteristics of the milk (200), ie, homogenization reduces the size of fat globules, which may then permeate the intestinal wall more readily. Depending on the temperature and pasteurization time, different proteins are denaturated to a variable extent. The composition of milk has also changed with changes in breeds and feeding of cows. The per capita consumption of cow milk has decreased in Finland by ≈30% since the middle of the past century (201). If cow milk turns out to be diabetogenic, such an effect must be related either to alterations in its composition or to modified human immune responses, because of changes in gut microbial flora and nutritional status. The prevalence of obesity has increased linearly in many populations and could contribute to the increasing trends in the incidence of not only type 2 but also of type 1 diabetes.

CONCLUDING REMARKS

Future studies on the role of dietary factors in the development of type 1 diabetes face a series of challenges. Longitudinal studies starting during pregnancy, proceeding through the development of preclinical type 1 diabetes, and ending at the time that the disease is diagnosed are needed to generate new reliable information on the possible contribution of dietary factors to progressive β cell destruction. Food consumption methods need to be developed for use in infants, children, and adolescents. How to reliably compare data from international multicenter studies that assess the effect of dietary factors on the pathogenesis of type 1 diabetes is a major issue that needs to be resolved.

Limited efforts have thus far been directed at studying nutritional risk predictors of type 1 diabetes. If a nutritional factor is confirmed to protect against or predispose to type 1 diabetes, the dietary exposure to that factor can be manipulated as a means of preventing the disease. Such a preventive measure could, in contrast with immunomodulatory therapy, be implemented relatively easily at the population level to maximize its effectiveness.

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