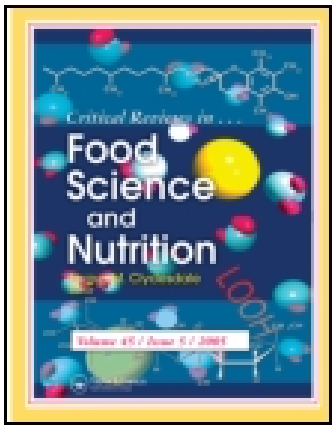

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Investigation of the Putative Associations Between Dairy Consumption and Incidence of Type 1 and Type 2 Diabetes

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A growing body of evidence suggests a possible relationship between the consumption of dairy products and the incidence of diabetes. A positive correlation between the early introduction of dairy in infancy and the incidence of type 1 diabetes (T1D) in genetically predisposed infants has been suggested by studies on rodents and humans. However, the lines of evidence supporting this association, including epidemiological studies and the observation of antibodies to bovine serum albumin, β-casein and bovine insulin in the serum of patients with T1D, are not without controversy. On the other hand, an inverse relationship between the consumption of dairy foods and the development of metabolic syndrome and/or type 2 diabetes (T2D) has been implied by epidemiological studies. Several dairy components, especially milk proteins, are believed to play a role in the beneficial effect of dairy consumption on glucose regulation by modulation of incretin hormones. Other dietary factors have also been associated with the incidence of T1D and T2D, indicating that dairy foods might be only one among many dietary agents possibly implicated in the development of diabetes. The present paper critically reviews the evidence and plausible mechanisms for the putative associations between dairy food consumption and incidence of T1D and T2D.

Keywords Diabetogenicity, β-cell autoimmunity, glycemic regulation, infant feeding, milk components

INTRODUCTION

The incidence of type 1 diabetes (T1D) and type 2 diabetes (T2D) is rising considerably worldwide (Wild et al., 2004). It is estimated that 285 million people are currently affected by diabetes and that each year seven million new cases of diabetes are diagnosed (Canadian Diabetes Association, 2011). To explain the increasing prevalence of diabetes, several hypotheses have been put forward that involve the consumption of dairy foods. These hypotheses are based on studies that suggest a positive correlation between the consumption of dairy products and T1D on the one hand, and an inverse relationship between dairy product consumption and T2D on the other hand, and have fuelled what has been referred to as "the milk debate" (King, 2005).

Type 1 diabetes, also referred to as insulin-dependent diabetes mellitus (IDDM), is an autoimmune disease usually occurring early in life in individuals presenting an inherited genetic susceptibility (Merriman, 2009). This disorder results in the attack and destruction of the insulin-producing β-cells of the pancreas by T lymphocytes (Åkerblom et al., 2002), leading to the incapacity of the pancreas to produce the required insulin to maintain normal blood glucose levels (Merriman, 2009). The occurrence of T1D has escalated in the Westernized world during the past two or three generations, reaching an annual worldwide increase of about 2.8% in the 1990s (The DIAMOND Project Group, 2006). This significant increase is suggested to be indirect evidence that environmental factors play an important role in T1D, and among the major putative environment factors, the early exposure to cow's milk proteins has particularly attracted the attention of the scientific community (Åkerblom et al., 2002). The current data do not reach the conclusion that cow's milk as such causes diabetes, but increasing evidence from studies on rodents and humans suggests that the pathogenic mechanisms linking the exposure to cow's milk proteins with the development of T1D could be related to the regulation of oral tolerance (Harrison and Honeyman, 1999; Kolb and Pozzilli, 1999; Wasmuth and Kolb, 2000; Åkerblom et al., 2002).

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On the other hand, T2D is a chronic metabolic disease representing 90–95% of all cases of diabetes in individuals over 20 years of age, and is characterized by the occurrence of fasting as well as postprandial hyperglycemia (Sebokova et al., 2007). It is believed that hyperglycemia in T2D is caused by several factors, such as a dysfunction of the pancreatic β-cells, insulin resistance or deficiency in insulin secretion, as well as being the result of an increase in hepatic glucose production (Sebokova et al., 2007). T2D is an increasing problem worldwide and it is estimated that the number of people with diabetes will reach 300 million worldwide by 2025 (Choi et al., 2005). An inverse association between the consumption of dairy products and/or dairy components and the incidence of T2D as well as the development of the metabolic syndrome (also known as insulin resistance syndrome) has been observed in several observational studies (Pereira et al., 2002; Elwood et al., 2008; Tremblay and Gilbert, 2009). This beneficial effect of dairy foods has been attributed to many dairy components, such as medium chain fatty acids, whey proteins, calcium, and other minerals (Pfeuffer and Schrezenmeir, 2006), and more recently to monounsaturated fatty acids such as palmitoleic acid (Mozaffarian et al., 2010).

The aim of this review is to examine the reported evidence and plausible mechanisms for the associations between dairy product consumption and incidence of T1D and T2D.

COW'S MILK CONSUMPTION AND TYPE 1 DIABETES: POSSIBLE ASSOCIATIONS

While the genetic susceptibility to diabetes is inherited, environmental factors such as diet or enteroviral infections are believed to have an important influence on whether the disease will actually be expressed in genetically predisposed individuals (Åkerblom et al., 2002; MacFarlane et al., 2003). One of the dietary factors suggested to play a role in the development of T1D is the early introduction in infancy of cow's milk into the diet. In fact, it was the observation of an inverse association between incidence of IDDM and breast-feeding from population data and case-control data in Norway, Sweden, and Denmark (Borch-Johnsen et al., 1984) that led to further research to explore the role of infant feeding in the etiology of T1D.

Over the last few decades, numerous studies have looked into the effects of early introduction of cow's milk protein on the risk of T1D and β-cell autoimmunity. The findings of these studies, however, have been inconsistent, with some reporting an increased risk of diabetes (Scott, 1990; Dahl-Jørgensen et al., 1991; Virtanen et al., 1993; Fava et al., 1994; Gerstein, 1994; Norris and Scott, 1996; Muntoni et al., 2000; Thorsdottir and Ramel, 2003; Rosenbauer et al., 2007) or β-cell autoimmunity (Kimpimäki et al., 2001; Holmberg et al., 2007) in children exposed to cow's milk, while others have reported no correlation (Norris et al., 1996; Couper et al., 1999; Esfarjani et al., 2001; Strotmeyer et al., 2004). Some of these studies are presented in the following sections. Selected to represent the range of human studies that have been conducted, including ecological, epidemiological, case control, prospective and retrospective cohort, as well as intervention studies, they serve to illustrate the inconsistent outcomes and complexity underlying the association between dairy product consumption and T1D.

DATA FROM HUMAN STUDIES—COW'S MILK EXPOSURE AND INCIDENCE OF TYPE 1 DIABETES

Ecological and Epidemiological Studies

A correlation between the exposure to cow's milk and the incidence of T1D between and within countries has been found in several epidemiological and ecological studies (Scott, 1990; Dahl-Jørgensen et al., 1991; Fava et al., 1994; Muntoni et al., 2000; Thorsdottir and Ramel, 2003) (Table 1). Scott (1990) investigated the data on consumption of unfermented milk products from 13 countries and found a significant positive correlation with the incidence of T1D ($r = 0.86$; $p < 0.01$). Similarly, Dahl-Jørgensen et al. (1991) found a correlation ($r = 0.96$) between the consumption of fluid milk in 12 countries and age-standardized incidence rates of IDDM in children 0–14 years old. The risk of T1D in children 0–14 years of age of nine regions of Italy was also significantly correlated to cow's milk consumption ($r = 0.84$; $P < 0.004$); however, no correlation was found for cheese intake (Fava et al., 1994). Similar findings were obtained by Muntoni et al. (2000) who investigated the relationship between T1D in children and adolescents under 15 years of age from 40 countries and their dietary energy intake from major food groups. Dairy products were found to be predictors of elevated prevalence rates of T1D ($r = 0.80$; $P < 0.0001$) (Muntoni et al., 2000). However, nutritional data in this study were derived from the Food and Agriculture Organization's food balance sheets and thus, food intake may have been overestimated in wealthy countries.

More recently, Thorsdottir and Ramel (2003) studied the possible role of cow's milk in the etiology of T1D by investigating the food and nutrient intakes of 4,701 children and adolescents ranging from 10 to 16 years in age in relation to the incidence of diabetes in 11 European countries. The prevalence of T1D was significantly associated with daily intake of milk ($r = 0.829$; p 0.042) or animal products (including milk, meat, and eggs) ($r = 0.999$; p 0.001). However, these correlations were observed only when Icelandic data were excluded. The authors justified this exclusion on the controversial premise that Icelandic cow's milk is less diabetogenic than milk from other countries due to its different protein composition, particularly the β-casein fraction (Thorsdottir and Ramel, 2003).

Although in developed countries milk-based formula are often the first complementary food to which babies are exposed, the proportions of infants first exposed to cow's milk varies between countries and cultures. Moreover, the type of complementary feeding that infants who are not first introduced to milk-based formula receive also differs between nations (Knip et al., 2010). This may be an important confounder in the ecological and epidemiological studies that have investigated

Table 1 Ecological and epidemiological studies on the association between dairy product consumption and the incidence of type 1 diabetes

Study	Countries investigated	Dietary variables investigated	Association between dairy consumption and T1D[1]
Scott, 1990	Japan, France, German Democratic Republic, Austria, England, Canada, New Zealand, Netherlands, Denmark, USA, Norway, Sweden, Finland	Unfermented milk products	Unfermented milk products (+): $r = 0.86$, $p < 0.01$
Dahl-Jørgensen et al., 1991	Finland, Sweden, Norway, Great Britain, Denmark, United States, New Zealand, Netherlands, Canada, France, Israel, Japan	Fluid milk	Fluid milk (+) : $r = 0.96$
Fava et al., 1994	Italy	Fluid milk and cheese	Fluid milk (+) : $r = 0.829$, $P < 0.004$ Cheese: No association
Muntoni et al., 2000	Algeria, Sudan, Tanzania, Canada, United States, Cuba, Mexico, Puerto Rico, Brazil, Chile, Peru, Israel, Japan, Kuwait, Republic of Korea, Australia, New Zealand, Austria, Belgium, Bulgaria, Denmark, Finland, France, Germany, Greece, Hungary, Iceland, Italy, Latvia, Luxembourg, Malta, Netherlands, Norway, Poland, Portugal, Romania, Russia, Spain, Sweden, United Kingdom	Dietary energy from major food groups (meat, cereals, dairy products, fruit and vegetable)	Dairy products (+) : $r = 0.80$, $P < 0.0001$
Thorsdottir and Ramel, 2003[2]	Austria, Belgium, Denmark, Finland, Germany, Iceland, Ireland, Northern Ireland, Norway, Sweden, Switzerland	Dietary intake	Milk intake (+) : $r = 0.829$, p 0.042 Animal products[3] (+): $r = 0.999$, p 0.001

[1]Plus (+) signs refer to a positive association. [2]Result of analysis excluding Icelandic data. [3]Animal products include milk, meat, and eggs.

the link between the exposure to cow's milk and the risk of T1D. Dairy products are not the only dietary factors that have been linked to IDDM; meat products (Muntoni et al., 2000) as well as fruits and vegetables (Thorsdottir and Ramel, 2003) have also been associated with the disease.

Case-Control Studies

A positive association (odds ratio (OR) = 1.57, 95% confidence interval (CI) 1.19–2.07; *P* 0.10 for homogeneity) between the early exposure to cow's milk (before 3–4 months of age) and the incidence of T1D was found in a meta-analysis of 13 case-control studies (Gerstein, 1994). A further meta-analysis of 17 case-control studies by Norris and Scott (1996) revealed an analogous relationship between early infant diet and T1D. The summary of all studies showed a moderate effect for exposure to breast-milk substitutes (OR = 1.38, 95% CI 1.18–1.61) and cow's milk-based substitutes (OR = 1.61, 95% CI 1.31–1.98) before the first three months of life. The putative diabetogenicity of dairy product consumption in infancy was also observed in a Finnish nationwide case-control study in which children exposed to dairy before the age of two months were found to present a greater risk of diabetes compared to those receiving dairy products later (Virtanen et al., 1993) (Table 2). Over the last few decades, a trend toward a longer duration of breast-feeding and a delay in the introduction of supplementary milk feeding has been observed in several countries, including Finland. To assess whether these changes in feeding patterns have an impact on the association between the exposure to dairy foods and the incidence of T1D, Virtanen et al. (1993) also investigated the data from two birth year cohorts (1972–1979 versus 1980–1988). The authors reported no significant difference between the two cohorts in the relationship between the age at introduction of dairy products and the risk of T1D (≥2 months versus <2 months; OR = 0.64 and 0.46 for the 1972–1979 and the 1980–1988 cohorts, respectively), which suggests that this association was not affected by the changes in the feeding patterns in early infancy in Finland. In a recent study, Rosenbauer et al. (2007) investigated early infant feeding patterns as well as other environmental factors on the risk of T1D in children under five years of age in Germany. An increased risk of T1D was observed in children introduced to formula/cow's milk before five months of age compared to those exposed after five months of age (OR = 1.34, 95% CI 1.03–1.74; *P* 0.030). A short breast-feeding period was also found to be associated with an increased risk of T1D (<5 months versus ≥5 months; OR = 1.31, 95% CI 1.01–1.69; *P* 0.039).

On the other hand, the influence of the exposure to cow's milk on the incidence of T1D was not observed in all case-control studies (Table 2). Esfarjani et al. (2001) reported no relationship between early cow's milk exposure and T1D in 52 IDDM patients and controls from Tehran. Moreover, in a larger study by Strotmeyer et al. (2004), in which the effects of dietary exposure during the first year of life on the risk of diabetes was investigated using data collected for 247 Chinese infants with T1D and 443 controls, cow's milk consumption was not associated with T1D before six months of age, whereas a negative association was observed between the seventh and 12th month of life (OR = 0.60, 95% CI 0.43–0.85; *P* 0.004).

Several factors may account for the discrepancy observed in these retrospective studies. The data on breast-feeding duration and age at introduction of cow's milk or other food products rely on parental recall, which can be inaccurate or biased especially

Table 2 Case-control studies on infant-feeding and the incidence of type 1 diabetes

Study	Location	Age of cases and controls	Number of cases and controls	Selection of controls	Elements of the diet assessment questionnaire	Results[1]
Virtanen et al., 1993	Finland	<15 years of age	690 case-control pairs	Birth-date-matched and sex-matched from the Finnish national population registry	Duration (overall and exclusive) of breast-feeding, age at introduction of supplementary milk feeding and solid foods, type of supplementary milk	Dairy exposure <2 months of age (+)
Esfarjani et al., 2001	Tehran	1.5–14 years of age	52 case-control pairs	Sex, age, social status, and geographical location matched from children at the outpatient pediatric clinic	Duration (overall and exclusive) of breast-feeding, age at introduction of dietary products including formula, cow's milk and solid foods	No relationship between early exposure to cow's milk and T1D
Strotmeyer et al., 2004	China	<15 years of age	247 cases and 443 controls	Sex, age (± 5 years), ethnic group, area of residence matched from hospital administration for injuries/minor surgery and locally resident populations	Intake of milk (breast milk and breast-milk substitutes) and food (rice, eggs, meat, fruit, vegetables, steamed bread, fish, noodles, and others)	No relationship between cow's milk consumption <six months of age and T1D Cow's milk consumption between 7 and 12 months of age (−): OR = 0.60, 95% CI 0.43–0.85, *P* 0.004
Rosenbauer et al., 2007	Germany	<5 years of age	749 cases and 624 controls	Children from the acquaintances of case families	Duration (overall) of breast-feeding, age at introduction of breast-milk substitutes and solid food, type of breast-milk substitutes, current level of customary cow's milk intake	Exposure to formula/cow's milk <5 months of age (+): OR = 1.34, 95% CI = 1.03–1.74, *P* 0.030

[1]Plus (+) signs refer to a positive association with T1D; minus (−) sign refers to a negative association with T1D.

when the length of the recall is long (Norris and Scott, 1996; Rosenbauer et al., 2007). Moreover, it has been suggested that mothers of children affected by T1D may have a biased recall of their child's diet compared with those whose child does not have T1D (Norris and Scott, 1996; Strotmeyer et al., 2004). Differences in the response rate of cases and controls may also introduce variability (Norris and Scott, 1996). Numerous studies failed to define whether "breast-feeding duration" referred to exclusive breast-feeding or overall breast-feeding, and often did not specify whether breast-feeding was stopped completely at the age that cow's milk was reported to be first introduced into the infant's diet. These aspects may also be a source of discrepancy.

DATA FROM HUMAN STUDIES—COW'S MILK EXPOSURE AND β -CELL AUTOIMMUNITY

The presence of diabetes-associated autoantibodies, including islet cell antibodies (ICA), insulin autoantibodies (IAA), glutamic acid decarboxylase antibodies (GADA), and tyrosine phosphatase-like protein IA-2 antibodies (IA-2A), is the first noticeable sign of emerging β-cell autoimmunity during the period preceding the manifestation of the disease (Virtanen and Knip, 2003). The occurrence of two or more types of these antibodies significantly increases the risk of progression to T1D (Couper et al., 1999; Knip et al., 2010). Positivity for diabetes-associated autoantibodies has been used as a surrogate marker of clinical T1D in prospective studies that have looked at the effects of infant feeding patterns on the incidence of the disease. These studies (Table 3), like those which have investigated the effects of cow's milk protein on the incidence of T1D, have produced contradictory outcomes (Virtanen and Knip, 2003).

Observational Studies

Kimpimäki et al. (2001) investigated the relation between early infant feeding and signs of β-cell autoimmunity in 2,949 infants with increased genetic risk of T1D in the Finnish Type 1 Diabetes Prediction and Prevention (DIPP) birth cohort. Analyses of ORs with CIs were based on a case-control study comprising 65 cases (who showed islet cell antibody positivity before four years of age) and 390 controls (who were islet cell antibody-negative) selected from the cohort. Children who first received cow's milk before two months of age or between 2 and 3.9

Table 3 Cohort studies on infant-feeding and the development of diabetes-associated autoantibodies

Study	Location	Design of the cohort (follow-up, months or years)	Number of children	Diabetes-associated autoantibodies investigated[1]	Association between age of first exposure to cow's milk and positivity for diabetes-associated autoantibodies[2]	External factors/adjustments
Norris et al., 1996	United States	Diabetes Autoimmunity Study in the Young (DAISY)[3]	18 cases and 153 controls	IAA, GADA, IA-2A	<3 months of age = no association <6 months of age = no association	Maternal age at birth and maternal diabetes status
Couper et al., 1999	Australia	The Australian Baby DIAB Study (median 29 months)	317	IAA, GADA, IA-2A	No association	NA[4]
Kimpimäki et al., 2001	Finland	The Finnish Type I Diabetes Prediction and Prevalence (DIPP) Study (4 years)	65 cases and 390 controls	ICA, IAA, GADA, IA-2A	<2 months of age (+): OR = 9.46, 95% CI 1.50–59.8, p 0.017 for all four autoantibodies 2–3.9 months of age (+): OR = 17.9, 95% CI 1.87–172, p 0.012 for all four autoantibodies	Mother's age and duration of education, relative height and weight at 12 months of age
Holmberg et al., 2007	Sweden	All Babies in Southeast Sweden (ABIS) Study (5–6 years)	3,776	IAA, GADA, IA-2A	1–3 months of age (+): OR = 1.84, 95% CI 1.01–3.37, P 0.047 for IAA, GADA, and/or IA-2A	Mother's age and duration education, infections during pregnancy, delivery mode, low birth weight (<2,500 g), early age of gestation (≤37 weeks), first-degree relative with T1D, coeliac disease or T2D, gastroenteritis

[1]IAA = insulin autoantibodies; GADA = glutamic acid decarboxylase antibodies; IA-2A = tyrosine phosphatase-like protein IA-2 antibodies; ICA = islet cell antibodies. [2]Plus (+) signs refer to a positive association with development of β-cell autoimmunity. [3]No follow-up period in the retrospective study by Norris et al. (1996). [4]No adjustments were mentioned by Couper et al. (1999).

months of age were found to have a higher risk of seroconversion to positivity for ICA, IAA, GADA, and IA-2A antibodies compared to those first introduced to cow's milk after the age of four months (OR = 9.46; CI 1.50–59.8; p 0.017, and OR = 17.9; CI 1.87–172; p 0.012, respectively).

A short duration of both total and exclusive breast-feeding, as well as the early introduction of cow's milk-based formula, was also associated with an increased risk of β-cell autoimmunity in children from the All Babies in Southeast Sweden (ABIS) Study (Holmberg et al., 2007). In this prospective study, 3,788 children from the general population were followed; 12 of these children developed T1D before 5–6 years of age and were not included in the analysis. The age at which infants were first exposed to formula was correlated with the duration of exclusive breast-feeding ($P < 0.000$), and the early exposure to formula (1–3 months of age) was associated with a higher risk of positivity for GADA, IAA, and/or IA-2A above the 99th percentile (OR = 1.84, 95% CI 1.01, 3.37; P 0.047) in the nondiabetic children at five years of age (Holmberg et al., 2007).

On the other hand, the early introduction of cow's milk protein was not found to be significantly associated with β-cell autoimmunity in 253 nondiabetic children in The Diabetes Autoimmunity Study in the Young (DAISY) (Norris et al., 1996). In this retrospective study, children selected were from 171 families with a member affected by T1D and between the ages of nine months and seven years when screened for β-cell autoimmunity (BCA). Among the 253 children studied, 18 cases of BCA were identified at baseline and 153 children without BCA were used as controls. No difference was found in the proportion of cases and controls who were introduced to cow's milk before three months or six months of age. Similar findings were reported by Couper et al. (1999) who prospectively followed, from birth for a median of 29 months, 317 children with a first-degree relative with T1D of The Australian Baby DIAB Study. The authors found no association between the development of β-cell autoimmunity and the introduction of cow's milk in these high-risk children.

The possible role of the mother's diet during pregnancy in the development of β-cell autoimmunity in the offspring has also been investigated. In a recent prospective cohort study by Virtanen et al. (2011), the authors assessed whether food consumption of mothers during pregnancy was associated with the development of islet cell antibodies and other diabetes-associated autoantibodies in children with increased human leukocyte antigen (HLA)-DQB1-conferred risk of T1D. No association was found between the maternal intake of milk and dairy products and β-cell autoimmunity in the infant. Moreover, no relationship between the maternal diet during pregnancy and the incidence of diabetes-associated autoantibodies was found in a randomized trial in which the mothers' diet either contained or did not contain cow's milk during the last trimester of their pregnancy (Ludvigsson, 2003). Similarly, maternal diet during the third trimester was not associated with islet autoimmunity in children from the DAISY birth cohort presenting a high- and moderate-risk HLA genotype (Lamb et al., 2008).

Ongoing International Prospective Studies

The Trial to Reduce IDDM in the Genetically at RISK (TRIGR) is the only dietary intervention trial that has been carried out to date to monitor the effects of early nutritional intervention on markers of β-cell autoimmunity and progression to T1D. Although the TRIGR study is still ongoing to follow the outcomes in terms of overt T1D, the effects of the intervention on markers of β-cell autoimmunity have been recently published (Knip et al., 2010). In this double-blind, randomized trial, 230 Finnish infants presenting increased risk of T1D were assigned at weaning either a highly hydrolyzed formula ("intervention," containing extensively hydrolyzed casein) or a regular cow's milk-based formula ("control," containing 80% intact milk protein and 20% hydrolyzed milk protein). Breast-feeding was encouraged until weaning, and the study formulae were available until the infants were eight months of age. Study subjects were followed up with respect to β-cell autoimmunity as well as progression to overt diabetes during a mean period of 4.7 years. In comparison to the control, the intervention was shown to present a protective effect against positivity to at least one diabetes-associated autoantibodies (after adjustment for the duration of exposure to the study formula, HR = 0.51, 95% CI 0.28–0.91; P 0.02). On the other hand, no significant association was found between the risk of T1D and the feeding intervention (after adjustment for the duration of exposure to the study formula, HR = 0.48, 95% CI 0.14–1.61) (Knip et al., 2010). However, it should be noted that this study was not designed with clinical T1D as the primary end point (Knip et al., 2010), and thus information regarding feasibility of early nutritional intervention to reduce risk of T1D awaits the larger ongoing TRIGR study involving 2,160 children from 15 countries, the results of which are expected to be available in the year 2017 (TRIGR, 2011).

In addition to the TRIGR study, another international prospective study, The Environmental Determinants of Diabetes in the Young (TEDDY), is currently underway. The TEDDY study consortium encompasses six clinical centers in the United States, Germany, Sweden, and Finland, whose goal is to identify environmental factors (infectious agents, dietary factors, psychosocial, and other factors), which either trigger or protect against the development of islet autoimmunity and T1D (TEDDY Study Group, 2008). To meet this goal, from 2004 to 2009, the TEDDY group has screened newborns from both the general population and high-risk families; the prospective follow-up study is underway and will continue until the subjects reach 15 years of age.

It is anticipated that the information from the findings of the TRIGR and the TEDDY prospective studies, which will become available in the next two decades, will provide useful insights to explain some of the present conflicting evidence on the role of

dietary factors and other environmental factors on the incidence of T1D.

DAIRY CONSUMPTION AND TYPE 1 DIABETES: POSSIBLE MECHANISMS

The hypothesis that dairy consumption is associated with risk of developing T1D has evolved from several lines of evidence, including the observation of antibodies to bovine serum albumin (BSA) (Persaud and Barranco-Mendoza, 2004), β-casein (Bell et al., 2006), and bovine insulin (Vaarala et al., 1998) in the serum of patients with T1D, as well as the isolation of T-cell lines specific to bovine β-casein in patients with T1D (Monetini et al., 2003). These observations have suggested that various constituents in bovine milk, including the A^1 variant of β-casein, BSA and insulin, may act as triggering agents in the development of T1D. A critical evaluation of these factors as well as the role of the gut mucosal immune function as potential mechanisms underlying the association of milk consumption with the risk of T1D is presented in the following sections.

Bovine A^1/A^2 β-Casein Variant

Caseins comprise approximately 80% of the proteins in bovine milk, and can be classified based on sequence homology into four families, namely α_{s1}-, α_{s2}-, β-, and κ-caseins, each with a number of genetic variants (Farrell et al., 2004). Among these, the A^1 variant of cow's milk β-casein has been suggested to play a role in the development of T1D.

Thirteen genetic variants of β-casein exist: A^1, A^2, A^3, B, C, D, E, F, G, H^1, H^2, I, (Farrell et al., 2004), and an A^4 allele, which has been found in Korean native cattle, but whose nucleotide substitution is not presently recognized (Kamiński et al., 2007). The A^1 and A^2 variants of β-casein are the most common in dairy cattle breeds, with the A^2 variant being more frequent in breeds such as Simmental, Jersey, and Guernsey (Bell et al., 2006), which are especially predominant in Central and Southern Europe. On the other hand, the A^1 variant predominates in Northern Europe and North America, where the black- and red-and-white breeds like Ayrshire, Holstein, and Friesian are the most common (Laugesen and Elliott, 2003; Bell et al., 2006; Merriman, 2009). In the United States, the Holstein breed, which produces milk containing about 42–62% A^1 variant in the β-casein fraction (De Noni et al., 2009), represents about 92% of the dairy cows, whereas the Guernsey breed, which produces milk containing 96–98% A^2 variant in the β-casein fraction (De Noni et al., 2009), account for only 1% (Bell et al., 2006). The Holstein breed is also the most common dairy breed in Canada, representing about 93% of the dairy herd (Canadian Dairy Information Center, 2010). Thus, the North American population consumes high levels of the A^1 variant of β-casein.

The A^1 and A^2 variants differ according to the amino acid located in position 67 of the β-casein molecule: a proline is present in the A^2 variant, whereas a histidine occupies this position in the A^1 form (Table 4). The enzymatic digestion of the A^1 variant by gastrointestinal proteases leads to the liberation of a seven-residue peptide with the following sequence: ^{60}Tyr-Pro-Phe-Pro-Gly-Pro-Ile^{66}. This β-casomorphin 7 peptide, which is not released from the A^2 variant, presents opioid properties and is believed to have an impact on mucus secretion, gut motility, and gene expression, as well as to influence lymphocyte proliferation (Kamiński et al., 2007; Merriman, 2009). It has been suggested that the A^1 form of β-casein could play a role in the development of T1D in addition to representing a risk factor for cardiovascular disease, sudden infant death syndrome, and neurological disorders such as schizophrenia and autism (Bell et al., 2006; Kamiński et al., 2007). By acting as an immune suppressant, it has been hypothesized that β-casomorphin 7 disturbs the gut-associated immune tolerance or reduces the patient's defense toward enterovirus, which is reported to be a possible cause of the development of T1D in genetically predisposed individuals (Kamiński et al., 2007).

The foundation of the hypothesis that A^1 β-casein is linked to T1D rests on epidemiological data that showed a positive correlation between the consumption of cow's milk containing A^1 β-casein and the incidence of T1D in 14-year-old children in 19 countries (Elliott et al., 1999; Laugesen and Elliott,

Table 4 Differences in amino acid sequences of β-casein variants. (Adapted from Kamiński et al., 2007)

	Amino acid at sequence position													
β-casein variant	18	25	35	36	37	67	72	88	93	106	117	122	137	138
A^1	Ser-P	Arg	Ser-P	Glu	Glu	His	Glu	Leu	Gln	His	Gln	Ser	Leu	Pro
A^2						Pro								
A^3						Pro				Gln				
B												Arg		
C			Ser		Lys									
D	Lys					Pro								
E				Lys		Pro								
F														Leu
G												Leu		
H^1		Cys				Pro		Ile						
H^2						Pro	Glu		Leu					Glu
I						Pro			Leu					

2003). This epidemiological association is not without controversy (Truswell, 2006; De Noni et al., 2009). One of the major criticisms is the weakening of the correlation by the inclusion of cheese-derived A^1 β-casein, instead of considering only milk and cream as sources of A^1 β-casein. In fact, a recent study by De Noni and Cattaneo (2010) showed that the in vitro gastrointestinal digestion of cheeses, including varieties such as Cheddar, Gouda, and Brie, led to the release of β-casomorphin 7. Moreover, there is an uncertainty surrounding the measurement of A^1 β-casein consumption. As pointed out by Truswell (2006), using data based on adult *per capita* consumption of milk is not ideal in the context of T1D, which usually occurs early in life, since most of the non-breast-fed infants are fed with formulas that often are based on a high whey protein content and a reduced casein content. Moreover, the number of countries included in these studies was relatively small, mainly limited by the availability of complete data on breed composition and milk polymorphism, which weakens the robustness of the data. In fact, if Laugesen and Elliott (2003) had included in their analysis the consumption of A^1 β-casein from Sardinia, the country presenting the second highest worldwide incidence of T1D, the correlation coefficient between T1D and A^1 β-casein consumption would have been reduced from $r = 0.92$ to $r = 0.79$ (Merriman, 2009).

The biological evidence supporting the role of A^1 β-casein in T1D is also weak. In fact, the animal experiments on nonobese diabetic (NOD) mice failed to confirm that A^1 β-casein is more diabetogenic than the A^2 form (Beales et al., 2002). In human studies, the levels of specific antibodies to A^1 and A^2 β-casein were not significantly different in the sera of children with T1D versus their siblings, whereas a significant difference was observed between T1D patients and controls/parents as well as between their siblings and controls/parents. An inverse correlation of A^1 and A^2 β-casein antibody levels with age was also observed. These findings suggest that the differences in level of A^1 and A^2 antibodies between various groups of individuals may not be specific to T1D but instead may be linked to age. The latter finding might mirror an infant's underdeveloped immune system's poor tolerance of exogenous antigens, in contrast to any specific association between plasma level of β-casein autoantibodies and T1D (Merriman, 2009).

Human β-casein contains a sequence of seven amino acids (^{51}Tyr-Pro-Phe-Val-Glu-Pro-Ile^{57}), which are homologous to bovine β-casomorphin 7 (Jarmolowska et al., 2007; De Noni et al., 2009). Interestingly, Jarmolowska et al. (2007) have observed the presence of various levels of β-casomorphin 5 and β-casomorphin 7 in human milk depending on the stage of lactation, and this despite the presence of a proline residue in position 58 of the β-casein sequence. It should be noted that human and bovine β-casomorphin 7 differ by two amino acids, a proline and a glycine in the bovine sequence having been replaced by a valine and a glutamine in the human sequence, and that the opioid activity of human β-casomorphin 7 is reported to be weaker than the bovine form (Koch et al., 1985; Chruścińska et al., 1998). Nevertheless, the natural occurrence of β-casomorphin 7 in human milk challenges the hypothesis that the release of β-casomorphin 7 from bovine milk during digestion is the cause of the positive correlation observed in epidemiological studies between the consumption of cow's milk containing A^1 β-casein and the incidence of T1D, and suggests that other factors might be responsible for the observed association.

Furthermore, the observation of a correlation between the incidence of T1D and latitude has led to the hypothesis that reduced sun exposure, correlated to latitude, and associated with a reduction of vitamin D intake, may be a risk factor in the development of T1D (Merriman, 2009). The administration of the active form of vitamin D (1, 25-dihydroxy vitamin D_3) was shown to reduce the incidence of diabetes and insulitis in NOD mice. The 1, 25-dihydroxy vitamin D_3 was also shown to modify T-cell differentiation, influence dendritic cell maturation toward the direction of a tolerogenic cell, and protect human pancreatic islets against cytokine-induce apoptosis (Mathieu and Badenhoop, 2005; Merriman, 2009). Several epidemiological studies have shown the protective effect of the active form of vitamin D against T1D (Mathieu and Badenhoop, 2005). Interestingly, the consumption of dairy products (including yogurt, cream, milk powder, as well as whole and skim milk) containing A^1 β-casein variant has also been associated with latitude. This raises the question about whether the observed association between A^1 β-casein consumption and incidence of T1D, as suggested by the epidemiological data, is confounded with latitude and vitamin D deficiency (Merriman, 2009).

Bovine Serum Albumin

Bovine serum albumin is a protein in the whey fraction of cow's milk that has also been suggested as a triggering agent in the development of T1D. This hypothesis was based on the observation of increased levels of immunoglobulin G (IgG) antibodies against BSA (Karjalainen et al., 1992; Hilger et al., 2001). Experimental studies have suggested that the anti-BSA antibodies seemed to be targeted against a segment of the milk protein called ABBOS, which includes the amino acid residues 152–168 (Persaud and Barranco-Mendoza, 2004). The BSA hypothesis rests on epitope mimicry between the ABBOS fragment and a 69-kDa protein present on the surface of the islet β-cells, known as p69, which induces an autoimmune response causing the destruction of pancreatic β-cells (Alting et al., 1999; Persaud and Barranco-Mendoza, 2004). According to this hypothesis, the introduction of cow's milk before three months of age, the age at which it is thought that the immune system is able to make the distinction between p69 and BSA, is linked to an increased risk of T1D (Persaud and Barranco-Mendoza, 2004).

This theory has been criticized because antibodies and abnormal T-cell responses to BSA in children with T1D have not been observed in all studies (Alting et al., 1999). Moreover, inconsistencies were found in the amino acid sequence reported as the ABBOS segment. Originally,

[1]Asp-Thr-His-Lys-Ser-Glu-Ile-Ala-His-Arg[10]-Phe-Lys-Asp-Leu-Gly-Glu-Glu-His-Phe-Lys[20]-Gly-Leu-Val-Leu-Ile-Ala-Phe-Ser-Gln-Tyr[30]-Leu-Gln-Gln-Cys-Pro-Phe-Asp-Glu-His-Val[40]-Lys-Leu-Val-Asn-Glu-Leu-Thr-Glu-Phe-Ala[50]-Lys-Thr-Cys-Val-Ala-Asp-Glu-Ser-His-Ala[60]-Gly-Cys-Glu-Lys-Ser-Leu-His-Thr-Leu-Phe[70]-Gly-Asp-Glu-Leu-Cys-Lys-Val-Ala-Ser-Leu[80]-Arg-Glu-Thr-Tyr-Gly-Asp-Met-Ala-Asp-Cys[90]-Cys-Glu-Lys-Gln-Glu-Pro-Glu-Arg-Asn-Glu[100]-Cys-Phe-Leu-Ser-His-Lys-Asp-Asp-Ser-Pro[110]-Asp-Leu-Pro-Lys-Leu-Lys-Pro-Asp-Pro-Ans[120]-Thr-Leu-Cys-Asp-Glu-Phe-Lys-Ala-Asp-Glu[130]-Lys-Lys-Phe-Trp-Gly-Lys-Tyr-Leu-Tyr-Glu[140]-Ile-Ala-Arg-Arg-His-Pro-Tyr-Phe-Tyr-Ala[150]-Pro-Glu-Leu-Leu-Tyr-Tyr-Ala-Asn-Lys-Tyr[160]-Asn-Gly-Val-Phe-Gln-Glu-Cys-Cys-Gln-Ala[170]-Glu-Asp-Lys-Gly-Ala-Cys-Leu-Leu-Pro-Lys[180]-Ile-Glu-Thr-Met-Arg-Glu-Lys-Val-Leu-Ala[190]-Ser-Ser-Ala-Arg-Gln-Arg-Leu-Arg-Cys-Ala[200]-Ser-Ile-Gln-Lys-Phe-Gly-Glu-Arg-Ala-Leu[210]-Lys-Ala-Trp-Ser-Val-Ala-Arg-Leu-Ser-Gln[220]-Lys-Phe-Pro-Lys-Ala-Glu-Phe-Val-Glu-Val[230]-Thr-Lys-Leu-Val-Thr-Asp-Leu-Thr-Lys-Val[240]-His-Lys-Glu-Cys-Cys-His-Gly-Asp-Leu-Leu[250]-Glu-Cys-Ala-Asp-Asp-Arg-Ala-Asp-Leu-Ala[260]-Lys-Try-Ile-Cys-Asp-Asn-Gly-Asp-Thr-Ile[270]-Ser-Ser-Lys-Leu-Lys-Glu-Cys-Cys-Asp-Lys[280]-Pro-Leu-Leu-Glu-Lys-Ser-His-Cys-Ile-Ala[290]-Glu-Val-Glu-Lys-Asp-Ala-Ile-Pro-Glu-Asn[300]-Leu-Pro-Pro-Leu-Thr-Ala-Asp-Phe-Ala-Glu[310]-Asp-Lys-Asp-Val-Cys-Lys-Asn-Tyr-Gln-Glu[320]-Ala-Lys-Asp-Ala-Phe-Leu-Gly-Ser-Phe-Leu[330]-Tyr-Glu-Tyr-Ser-Arg-Arg-His-Pro-Glu-Tyr[340]-Ala-Val-Ser-Val-Leu-Leu-Arg-Leu-Ala-Lys[350]-Glu-Tyr-Glu-Ala-Thr-Leu-Glu-Glu-Cys-Cys[360]-Ala-Lys-Asp-Asp-Pro-His-Ala-Cys-Tyr-Ser[370]-Thr-Val-Phe-Asp-Lys-Leu-Lys-His-Leu-Val[380]-Asp-Glu-Pro-Gln-Asn-Leu-Ile-Lys-Gln-Asn[390]-Cys-Asp-Gln-Phe-Glu-Lys-Leu-Gly-Glu-Tyr[400]-Gly-Phe-Gln-Asn-Ala-Leu-Ile-Val-Arg-Tyr[410]-Thr-Arg-Lys-Val-Pro-Gln-Val-Ser-Thr-Pro[420]-Thr-Leu-Val-Glu-Val-Ser-Arg-Ser-Leu-Gly[430]-Lys-Val-Gly-Thr-Arg-Cys-Cys-Thr-Lys-Pro[440]-Glu-Ser-Glu-Arg-Met-Pro-Cys-Thr-Glu-Asp[450]-Tyr-Leu-Ser-Leu-Ile-Leu-Asn-Arg-Leu-Cys[460]-Val-Leu-His-Glu-Lys-Thr-Pro-Val-Ser-Glu[470]-Lys-Val-Thr-Lys-Cys-Cys-Thr-Glu-Ser-Leu[480]-Val-Asn-Arg-Arg-Pro-Cys-Phe-Ser-Ala-Leu[490]-Thr-Pro-Asp-Glu-Thr-Tyr-Val-Pro-Lys-Ala[500]-phe-Asp-Glu-Lys-Leu-Phe-Thr-Phe-His-Ala[510]-Asp-Ile-Cys-Thr-Leu-Pro-Asp-Thr-Glu-Lys[520]-Gln-Ile-Lys-Lys-Gln-Thr-Ala-Leu-Val-Glu[530]-Leu-Leu-Lys-His-Lys-Pro-Lys-Ala-Thr-Glu[540]-Glu-Gln-Leu-Lys-Thr-Val-Met-Glu-Asn-Phe[550]-Val-Ala-Phe-Val-Asp-Lys-Cys-Cys-Ala-Ala[560]-Asp-Asp-Lys-Glu-Ala-Cys-Phe-Ala-Val-Glu[570]-Gly-Pro-Lys-Leu-Val-Val-Ser-Thr-Gln-Thr[580]-Ala-Leu-Ala[583]

Figure 1 Primary amino acid sequence of BSA. (Adapted from Farrell et al., 2004. The entry name and file number of the protein in the UniProt Knowledgebase of ExPASy Proteomics Server are ALBU-BOVIN and P02769). The ABBOS fragment sequences as reported by Robinson et al. (1993) (region 128–145, dotted line) and by Karjalainen et al. (1992) (region 152–169, solid line, incorporating the missing Tyr in the sequence updated by Hirayama et al., 1990) are also represented.

Karjalainen et al. (1992) identified 17 amino acid residues in the 152–168 region of BSA as the ABBOS section (i.e., [152]Glu-Leu-Leu-Tyr-Ala-Asn-Lys-Tyr-Asn-Gly-Val-Phe-Gln-Glu-Cys-Cys-Gln[168]), whereas Robinson et al. (1993) identified the ABBOS fragment as the 18 amino acids in position 128–145 (i.e., [128]Ala-Asp-Glu-Lys-Lys-Phe-Trp-Gly-Lys-Tyr-Leu-Tyr-Glu-Ile-Ala-Arg-Arg-His[145]) (Figure 1). However, the BSA amino acid sequence was updated following the discovery of a missing tyrosine residue in position 156 and the reversed order of the amino acids in positions 94 and 95 (Hirayama et al., 1990). Thus, the ABBOS peptide reported by Karjalainen et al. (1992) should have contained 18 amino acid residues with the sequence [152]Glu-Leu-Leu-Tyr-Tyr-Ala-Asn-Lys-Tyr-Asn-Gly-Val-Phe-Gln-Glu-Cys-Cys-Gln[169].

In order to trigger an anti-ABBOS immune response, the ABBOS peptide must remain intact in the gastrointestinal tract. As pointed out by Persaud and Barranco-Mendoza (2004), if the ABBOS peptide corresponds to the amino acids in positions 128–145, it is most likely that the peptide would be broken down by the enzyme trypsin since this enzyme acts on the carboxyl side of Lys and Arg residues and the region 128–145 contains many of these amino acids. Nevertheless, Alting et al. (1999) have found that an increase of the pH of the pepsin-catalyzed hydrolysis from 2 to 4 (corresponding to the condition prevailing in adult and young infant stomachs, respectively) significantly reduces the efficiency of the hydrolysis. Thus, it is possible that the ABBOS region of BSA remains intact in the gastrointestinal tract of very young infants because of the relatively high pH of the gut early in life and due to limited accessibility of the ABBOS peptide to proteolytic enzymes.

Three regions of similarity between human p69 and BSA were identified from the results reported by Pietropaolo et al. (1993) and Miyazaki et al. (1994); these homologous sequences were observed in the regions 127–132, 174–179, and 373–380 (Figure 2). Surprisingly, the regions of similarity between p69 and BSA do not correspond with the ABBOS region (152–169) suggested by Karjalainen et al. (1992), but one region does

1st region :
p69 = [39]Lys-Ala-Thr-Gly-Lys-Lys[44]
BSA = [127]Lys-Ala-Asp-Glu-Lys-Lys[132]

2nd region :
p69 = [205]Phe-Asp-Lys-Leu-Lys-Met-Asp-Val[212]
BSA = [373]Phe-Asp-Lys-Leu-Lys-His-Leu-Val[380]

3rd region :
p69 = [353]Gly-Ala-Cys-Leu-Gly-Pro[358]
BSA = [174]Gly-Ala-Cys-Leu-Leu-Pro[179]

Figure 2 Regions of similarity between human p69 and BSA sequences. (Adapted from Persaud and Barranco-Mendoza, 2004; the numbering of the amino acid fragments of BSA has been adapted to be in accordance with the BSA primary amino acid sequence shown in Fig. 1).

overlap with the ABBOS fragment (128–145) reported by Robinson et al. (1993).

Human serum albumin also shows some similarity to p69 and BSA, which means, according to the theory of cross reactivity and molecular mimicry proposed by Karjalainen et al. (1992), that antibodies against human serum albumin should also be produced. This complicates the theory linking BSA and T1D, and raises several questions, such as the level of similarity required in the sequence of p69 and BSA to trigger destruction of β-cells.

Anti-BSA antibodies have also been found in individuals presenting other autoimmune diseases, such as rheumatoid arthritis, which suggests that BSA may simply trigger a general immune response and that the presence of anti-BSA antibodies in patients with T1D may not be a β-cell specific immunity, but merely the reflection of a flawed process of immunologic tolerance associated with a predisposition to autoimmunity (Atkinson et al., 1993).

Cross Reactivity Between Bovine and Human Insulin

Insulin is believed to be the primary autoantigen occurring in T1D (Vaarala, 2002) and to play a major role in β-cell destruction as it is the sole β-cell-specific autoantigen in T1D (Harrison and Honeyman, 1999; Vaarala, 2002). Thus, the occurrence of autoantibodies to insulin (IAA) and islet cell antibodies (ICAs) is often used as a risk marker for T1D, as these autoantibodies are related to the impaired secretion of insulin by β-cells and usually precede the development of T1D. Studies have shown that the frequency of IAA varies from 20 to 60% in individuals with newly diagnosed T1D and from 1 to 10% in healthy subjects (Vaarala et al., 1998). A prospective cohort study on offspring of parents with T1D has shown that IAA appeared earlier and were detected more frequently than other autoantibodies (Ziegler et al., 1999), suggesting that immunization to insulin may be one of the earliest occurrences in the development of an autoimmune process against β-cells in individuals.

Thus, an alternative view of the role of cow's milk in T1D, other than mechanisms attributed to β-casein A^1 variant and BSA, is the possibility that bovine insulin may create cross-reactive immunity to human insulin (Vaarala et al., 1998). Bovine insulin differs from human insulin by only three amino acid residues, the difference being observed at position 8 and 10 in the A-chain and position 30 in the B-chain (Vaarala et al., 1998), and is reported to be immunogenic in humans (Reeves and Kelly, 1982). Vaarala et al. (1998) have demonstrated orally-induced immunization to bovine insulin. They measured IgG antibodies to human and bovine insulin in children fed with formula containing whole cow's milk protein, formula containing hydrolyzed casein, or breast-fed during the first months of their life. They observed that, at six months of age, the infants who received cow's milk formula presented higher levels of IgG antibodies to bovine insulin compared to those who received hydrolyzed casein peptides formula or who were exclusively breast-fed. Throughout the follow-up, a decrease of insulin-binding antibodies and T-cell responses seemed to occur in most of the infants, reflecting tolerance to the dietary antigens. On the other hand, bovine insulin-binding antibodies identified by enzyme immunoassay were shown to increase in children who developed diabetes-associated autoantibodies during a follow-up at 18 months from birth. These observations suggest that the insulin-specific immune response caused by dietary insulin in early infancy may not be regulated in infants who are susceptible to developing autoimmunity (Vaarala et al., 1998). Thus, the high incidence of insulin-binding antibodies in infants with T1D may be the result of oral immunization to bovine insulin contained in cow's milk formula.

Implication of the Gut Immune System in the Development of T1D—Are Dairy Proteins the Only Triggering Agents?

There is increasing evidence, in studies on rodents as well as on human beings, that the gut-associated immune system is a keystone in the development of autoimmune diseases, most likely due to disturbed oral tolerance mechanisms. Oral tolerance, which depends on the normal maturation and immunological homeostasis of the gut, may be influenced by several factors, such as gut flora, infection, growth factors, and cytokines provided by breast milk, as well as diet (Figure 3). All these factors may interfere with gut immune function and lead to immunization by oral antigens instead of tolerance (Harrison and Honeyman, 1999; Kolb and Pozzilli, 1999; Wasmuth and Kolb, 2000; Vaarala, 2002).

Epidemiological studies, such as the Finnish birth cohort study, have suggested that short-term breast-feeding and the early introduction of cow's milk-based infant formula was associated with the risk of developing β-cell autoimmunity in young children presenting a genetic predisposition to T1D (Kimpimäki et al., 2001). These observations are consistent with the hypothesis presented more than two decades earlier by Borch-Johnsen et al. (1984), from their investigation of the relation between breast-feeding and incidence rates of IDDM of children in three Scandinavian countries, that it is not the introduction of cow's milk into the diet per se, but the lack of breast milk that may have detrimental consequences for at-risk individuals. Breast milk is known to contain a variety of growth factors and cytokines, which are believed to play a role in the maturation of the gut-associated lymphoid tissue (Srivastava et al., 1996), whereas these compounds are almost nonexistent in cow's milk-based infant formulae (Kolb and Pozzilli, 1999). It is hypothesized that a lack of these factors may hinder the development of mucosa-mediated tolerance to islet autoantigens, including insulin present in breast milk or cross-reactive epitopes (Harrison and Honeyman, 1999). Moreover, a lack of passively transferred maternal immunity is believed to predispose infants to enteric infections. It is possible that enteroviral infections, by increasing intestinal permeability or by disturbing mucosal immunity, may contribute to an increase in the exposure to dietary antigens and a higher incidence of autoimmune reactions (Harrison and Honeyman, 1999; Wasmuth and Kolb, 2000).

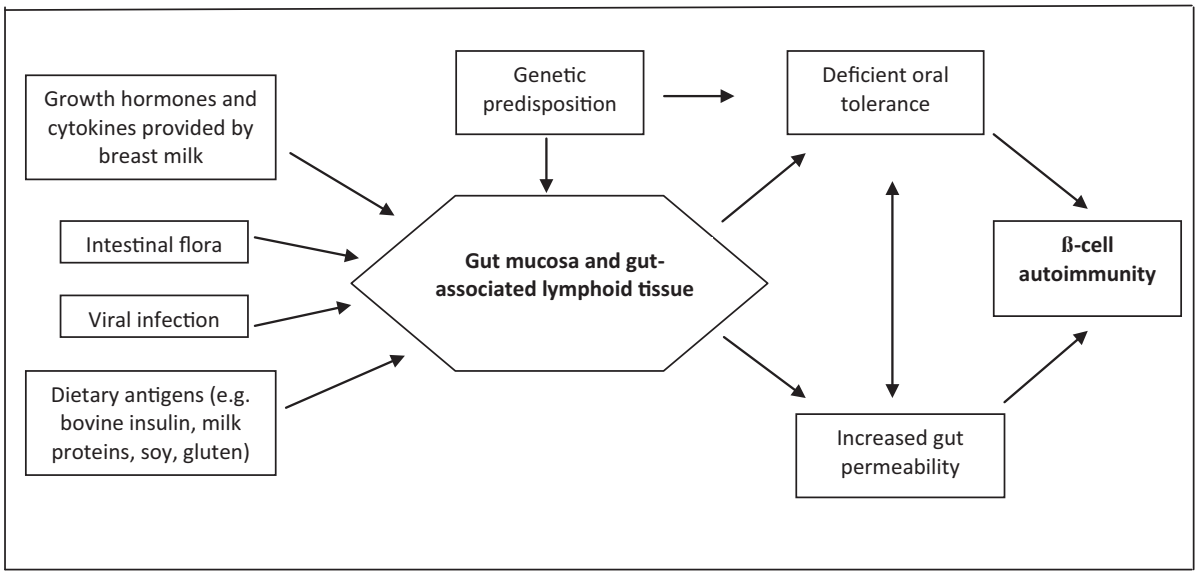

Figure 3 Factors playing roles in gut maturation and the possible implication of the gut immune system in the development of T1D. (Adapted from Wasmuth and Kolb, 2000).

Newborn babies, especially preterm infants, present an increased intestinal permeability, and this can result in unwanted large molecules and infectious agents to enter the bloodstream and trigger the development of inflammation, infection, and systemic hypersensitivity (van Elburg et al., 2003; Colomé et al., 2007). Several factors, such as gestational and postnatal age, as well as the feeding method have been proposed to have an impact on the maturation of the small intestine mucosa, leading to a decrease in gut permeability (van Elburg et al., 2003; Colomé et al., 2007). Maturation of the intestinal mucosa is required to promote normal immunity and tolerance (Insoft et al., 1996). An increased intestinal permeability has been suggested to play a role in the development of several autoimmune diseases such as T1D by enhancing immune activation and thus triggering autoimmunity (Vaarala, 2008; Visser et al., 2009).

Cow's milk proteins are usually the first dietary antigen encountered by the body, but other dietary proteins may also lead to an increased immunity in individuals predisposed to T1D (Harrison and Honeyman, 1999; Wasmuth and Kolb, 2000). Animal studies in which NOD mice and diabetes-prone BioBreeding (BBdp) rats were fed with different dietary proteins have shown that the source of protein has a major impact on the development of T1D and that not only milk but also soy and wheat may act as promoting agents in the development of T1D (Scott, 1996; Lefebvre et al., 2006). In fact, a blind, multicenter (New Zealand, Canada, and United Kingdom) study showed that a wheat-based, milk free-diet resulted in the highest diabetes incidence in NOD mice and BBdp rats (Beales et al., 2002). This finding supports previous studies reporting a higher occurrence of spontaneous diabetes in animals fed with plant-based diets presenting a high content of wheat (Scott, 1996; MacFarlane et al., 2003).

The role of wheat proteins in the pathogenesis of T1D has also been supported by several prospective studies. Moreover, the timing of initial exposure to dietary proteins during infancy may play a role on islet autoimmunity risk in predisposed children. The BABYDIAB study, a cohort study conducted from 1989 to 2003 following 1,610 newborn children of parents with T1D, showed that the early introduction (before three months of age) of gluten into the diet was associated with an increased risk of development of islet autoantibodies. However, no increased risk of islet autoantibodies was observed when gluten was introduced after the age of six months (Ziegler et al., 2003). On the other hand, the DAISY birth cohort study, in which 1,183 children at increased risk of T1D were followed for nine months to nine years, showed that infants exposed to cereals between 0 and 3 months or after the age of seven months presented an increased risk of developing islet autoantibodies (Norris et al., 2003). The consumption of soy milk formula was also found to be associated with an increased risk of T1D in Chinese infants in a prospective study by Strotmeyer et al. (2004). In fact, the exposure to soy milk formula from 4 to 6 months of age was shown to result in a doubling of the risk of T1D whereas the consumption of soy milk formula from 7 to 12 months of age was associated with a 50% higher risk (OR = 2.0, 95% CI 1.1–3.4; *P* 0.02 and OR = 1.5, 95% CI 1.0–2.1; *P* 0.05, respectively).

These results reinforce the belief that individuals predisposed to T1D may have an impaired mucosa-mediated tolerance and thus present an enhanced autoimmunity to dietary proteins in general and not specifically to dairy proteins.

DAIRY FOOD INTAKE AND TYPE 2 DIABETES: POSSIBLE ASSOCIATIONS

It is known that diet plays an important role in the prevention and management of metabolic syndrome, which is a

combination of various metabolic disturbances, including abdominal obesity, insulin resistance, hypertension, impaired endothelial and hemostatic function, and atherogenic dyslipidemia, that strongly increase the risk of developing T2D and cardiovascular disease (Mensink, 2006; van Meijl et al., 2008). Over the past decade, several cohort studies have investigated the relationship between dairy food consumption and the risk of the metabolic syndrome and/or T2D, by analyzing either the dairy food intake per se or dietary patterns that included dairy products and the incidence of metabolic syndrome and/or T2D in the study population. Overall, as presented in the following sections, these studies have indicated that the consumption of dairy foods is associated with a reduced risk of T2D. The mechanisms underlying this association are still unclear, but various dairy components, including the protein and fat fractions as well as the content of vitamin D, calcium, and other minerals, have been suggested to contribute to the perceived beneficial effects of dairy foods on reducing the risk of developing T2D and on blood glucose regulation.

DATA FROM OBSERVATIONAL STUDIES—ASSOCIATION BETWEEN DAIRY FOOD INTAKE AND TYPE 2 DIABETES

A growing body of evidence from observational studies has suggested, with a few exceptions, an inverse association between the consumption of dairy food and the metabolic syndrome (Elwood et al., 2008; Tremblay and Gilbert, 2009). The type of dairy foods and their fat and nutrient contents are some of the main factors suggested to have an impact on the strength of the association. On the other hand, only a few studies have looked into the relationship between dairy consumption and the incidence of T2D (Table 5); thus, this relationship is not as clearly defined as it is for the metabolic syndrome.

Elwood et al. (2007) examined the association between dairy or milk intake and the metabolic syndrome in 2,375 men aged 45–59 years. In this study, the clinical importance of the syndrome on incident ischemic stroke, heart disease, and diabetes was investigated by a follow-up examination of the men at five-year intervals over about 20 years. Food consumption at baseline, including specifically milk and dairy foods, was assessed for all the men in the study using a semi-quantitative food frequency questionnaire (FFQ). In addition, a representative sample of 640 men kept a seven-day weighed dietary intake (WDI) record. In this sample, 89 men had the metabolic syndrome at baseline, and 41 developed diabetes during the follow-up period. The incidence of diabetes was significantly associated with criteria related to the metabolic syndrome, a relative risk (RR) of 4.09 (95% CI 2.92–5.74) being observed in men presenting two or more criteria.

Inverse relationships were observed for the consumption of both milk and dairy products and the metabolic syndrome at baseline (Elwood et al., 2007). Compared to men who affirmed drinking little or no milk as reported on the FFQ, men who consumed one pint or more of milk per day had an adjusted OR for the metabolic syndrome of 0.38 (95% CI 0.18–0.78; P_{trend} 0.002). Similar findings were obtained for the association between the metabolic syndrome and milk intake estimated from the WDI. Moreover, when considering the total dairy intake (defined as milk, cheese, yogurt, butter, and cream), an OR for the syndrome of 0.44 (95% CI 0.21–0.91; P_{trend} 0.023) was found in the quarter of men with the highest dairy food intake based on the WDI. The data of the WDI also suggested a lower incidence of T2D in men with the highest quarter of milk intake. However, this association was not significant and, as pointed out by the authors, it was not possible to draw a clear conclusion on the association between milk intake and T2D due to the limited number of men in the WDI sample.

Data from two prospective cohort studies that have reported the incidence of T2D in relation to dairy consumption have shown a decrease in T2D incidence with each serving-per-day increase in dairy intake (Choi et al., 2005; Liu et al., 2006). The first study by Choi et al. (2005) prospectively examined the relationship between dairy consumption and incidence of T2D in 41,254 males who were aged 40–75 years when first recruited for the Health Professionals Follow-up Study. Using the data accumulated over 12 years, the RR of T2D for men in the top quintile of total dairy intake (i.e., 4.1 servings/day) was 0.77 (95% CI 0.62–0.95; P_{trend} 0.003) in comparison with those in the lowest quintile (i.e., 0.5 serving/day). The RR of T2D determined for low-fat dairy consumption was 0.73 (95% CI 0.59–0.89; P_{trend} 0.001) and for high-fat dairy foods was 0.97 (95% CI 0.78–1.21; P_{trend} 0.78). Each serving-per-day increase in total dairy intake was associated with a 9% lower risk for T2D in the men in this study.

Similar trends were reported by Liu et al. (2006) for 37,183 middle aged and older women from the Women's Health Study who were followed for about 10 years. After adjusting for potential confounding variables, they reported a RR for T2D of 0.79 (95% CI 0.67–0.94; P_{trend} 0.007) in the highest quintile (i.e., >2.9 servings/day) compared with women in the lowest quintile (i.e., <0.85 serving/day). A 4% lower risk of T2D was associated with each serving-per-day increase in dairy intake. The relationship between dairy consumption and the incidence of T2D did not change after adjustment for dietary calcium, vitamin D, glycemic load, fat, and fiber as well as magnesium intake (RR = 0.68; 95% CI 0.52–0.89; P_{trend} 0.006). The inverse association was shown to be essentially due to the consumption of low-fat dairy foods, the RRs comparing the highest to the lowest quintiles being 0.79 (95% CI 0.67–0.93; P_{trend} 0.002) and 1.05 (95% CI 0.88–1.24; P_{trend} 0.44) for low-fat and high-fat foods, respectively.

In these two studies of male and female health professionals (Choi et al., 2005; Liu et al., 2006, respectively), the negative relationship between dairy food intake and the incidence of T2D seemed to be mainly resulting from low-fat dairy products, with a lower RR of developing T2D being associated with intake of either total or low-fat dairy foods (skim/low-fat milk, yogurt, cottage/ricotta cheese, and/or sherbet), but not high-fat dairy

Table 5 Observational studies on the association between dairy intake and type 2 diabetes

Study	Number and gender of subjects	Location	Design of the Cohort (follow-up, years)	Dairy intake (servings/day)[1] (lowest and highest amount)	Results	Adjustments
Choi et al., 2005	41,254 men	United States	Health Professionals Follow-up cohort (HPFS) (12 years)	Total dairy: <0.9 and ≥2.9 Low-fat: <0.14 and >1.58 High-fat: <0.38 and >1.72	Total dairy: RR = 0.77, 95% CI 0.62–0.95, P_{trend} 0.003 Low-fat: RR = 0.73, 95% CI 0.59–0.89, P_{trend} 0.001 High-fat: RR = 0.97, 95% CI 0.78–1.21, P_{trend} 0.78	Age, BMI, total energy, smoking, high cholesterol, hypertension, diabetes history, alcohol, physical activity, follow-up time, certain dietary variables, fiber, glycemic load
Liu et al., 2006[2]	37,183 women	United States	Women's Health Study cohort (WHS) (10 years)	Total dairy: <0.85 and >2.9 Low-fat: ≤0.27 and >2.00 High-fat: <0.20 and >1.329	Total dairy: RR = 0.68, 95% CI 0.52–0.89, P_{trend} 0.006 Low-fat: RR = 0.69, 95% CI 0.52–0.91, P_{trend} 0.007 High-fat: RR = 0.99, 95% CI 0.82–1.20, P_{trend} 0.90	Age, BMI, total energy, smoking, high cholesterol. hypertension, diabetes history, alcohol, physical activity, hormone therapy, total fat, fiber, glycemic load, vitamin D, Ca, Mg
Pittas et al., 2006	83,779 women	United States	Nurses' Health Study (NHS) cohort (20 yrs)	Total dairy: <1.0 and >3.0	Total dairy: RR = 0.89, 95% CI 0.81–0.99 P_{trend} 0.008	Age, BMI, total energy, smoking, hypertension, diabetes history, alcohol, physical activity, type of fat, glycemic load, retinol, caffeine, fiber, Ca, vit. D
van Dam et al., 2006	41,186 black women	United States	Black Women's Health Study cohort (BWHS) (8 years)	Total dairy: 0.07 and 2.53 Low-fat: 0.00 and 1.22 High-fat: 0.07 and 1.33	Total dairy: HR = 0.93, 95% CI 0.75–1.15, P_{trend} 0.31 Low-fat: HR =0.87, 95% CI 0.76–1.00, P_{trend} 0.04 High-fat: HR = 1.03, 95% CI 0.88–1.20, P_{trend} 0.94	Age, BMI, total energy, smoking, physical activity, alcohol, diabetes history, education level, coffee, sugar-sweetened soft drink, meats
Elwood et al., 2007	640 men[3]	United Kingdom	The Caerphilly cohort (20 years)	Total milk: Highest 1/4	Total milk: RR = 0.57, 95% CI 0.20–1.63, P_{trend} 0.247	Age, BMI, smoking, social class
Kirii et al., 2009	25,877 men and 33,919 women	Japan	The Japan Public Health Center-based Prospective Study (JPHC) (5 years)	Total dairy: <50 and ≥300 Milk: <50 and ≥200 Cheese: 0 and ≥5 Yogurt: 0 and ≥60	Total dairy: OR = 0.71, 95% CI 0.51–0.98, P_{trend} 0.054 Milk: OR = 0.87, 95% CI 0.70–1.09, P_{trend} 0.16 Cheese: OR = 1.12, 95% CI 0.80–1.57, P_{trend} 0.56 Yogurt: OR = 0.77, 95% CI 0.58–1.01, P_{trend} 0.13	Age, BMI, total energy, smoking, hypertension, diabetes history, alcohol, physical activity, coffee, energy-adjusted magnesium, area

RR = relative risk; HR = hazard ratio; BMI = body mass index; Ca = calcium; vit. D = vitamin D; Mg = magnesium.
[1]Dairy intake shown as servings per day, except for Elwood et al. (2007) and Kirii et al. (2009) studies in which intakes were reported as quartiles and grams per day, respectively. [2]Results with multivariate model 3 adjustments. [3]Data from a food frequency questionnaire was available for 2,375 men, but only 640 men kept a seven-day weighed dietary intake record.

foods (whole milk, cream, sour cream, butter, ice cream, cream cheese, and/or other cheese). Moreover, in both studies the relationship was not significantly affected by BMI (i.e., <25 versus ≥25 kg/m^2). The reason for the weak or lack of association with high-fat dairy foods was not explained in either study; however, the presence of saturated fat in dairy foods was speculated by Liu et al. (2006) to be a potential factor in negating the benefits provided by the insulinotropic properties of milk proteins.

Findings from some human studies have suggested that higher intake of vitamin D (Isaia et al., 2001; Pittas et al., 2006), calcium (Pittas et al., 2006; van Dam et al., 2006), magnesium (Lopez-Ridaura et al., 2004; van Dam et al., 2006), and their major food sources, such as dairy products, may help to lower the risk of T2D. These findings propose that altered magnesium, calcium, and vitamin D homeostasis may have an impact on the development of T2D. van Dam et al. (2006) conducted an eight-year Black Women's Health Study on the association between the incidence of T2D and the magnesium and calcium intakes of 41,186 African–American women aged 21–69 years. They found a hazard ratio (HR) of T2D of 0.69 (95% CI 0.59–0.81; $P_{\text{trend}} < 0.0001$) for dietary magnesium and 0.86 (95% CI 0.74–1.00; P_{trend} 0.01) for dietary calcium for the highest (calcium: 661 mg/day; magnesium: 244 mg/day) compared with the lowest quintile (calcium: 219 mg/day; magnesium: 115 mg/day) intakes. When calcium and magnesium intakes were mutually adjusted, the relation for calcium was no longer observed (HR = 1.04; 95% CI 0.88–1.24; P_{trend} 0.88), but the association remained for magnesium. A daily consumption of low-fat dairy products was associated with a lower risk of T2D in comparison with the consumption of less than one serving per week (HR = 0.87; 95% CI 0.76–1.00; P_{trend} 0.04). Pittas et al. (2006) have also studied the association between vitamin D and calcium intakes and the risk of T2D. They followed 83,779 women (aged 30–55 years) from the Nurses' Health Study for 20 years. After adjustment for the various potential confounders, a 33% lower risk of T2D was observed for women with combined daily intakes of >1,200 mg calcium and >800 IU vitamin D with RR of 0.67 (95% CI 0.49–0.90), compared to those presenting combined intakes of ≤600 mg of calcium and ≤400 IU of vitamin D. Since dairy foods represent the major dietary source of vitamin D and calcium in the United States where the study was carried out, the authors also investigated, in a separate analysis, the relation between dairy intake and T2D. They found that women who consumed three or more servings per day, compared to those who consumed less than one serving per day of dairy products, had 11% lower risk of T2D (RR = 0.89; 95% CI 0.81–0.99; P_{trend} 0.008). However, the strength of this association was weakened (RR = 0.94; 95% CI 0.83–1.06; P_{trend} 0.12) after adjustment for total vitamin D and calcium intake.

In a recent prospective study by Kirii et al. (2009), in which 59,796 middle-aged and older women and men of the Japan Public Health Center-based Prospective Study were followed for a period of five years, calcium and vitamin D alone were not significantly associated with T2D in either men or women. However, among subjects who consumed a greater amount of vitamin D, intake of calcium was inversely associated with the incidence of diabetes (OR = 0.62; 95% CI 0.41–0.94; P_{trend} 0.050 and OR = 0.59; 95% CI 0.38–0.91; P_{trend} 0.043, for the highest versus the lowest quartiles of calcium intake in men and women, respectively). This finding suggests that these two nutrients may act in conjunction, and not independently, in reducing the risk of T2D. Moreover, a significant inverse relationship between total dairy food intake and the risk of T2D was found in women (OR = 0.65; 95% CI 0.49–0.88; P_{trend} 0.007, for the highest versus the lowest intake). However, the strength of this association was weakened after adjustment for several confounding factors including body mass index, total energy, and family history of diabetes (OR = 0.71; 95% CI 0.51–0.98; P_{trend} 0.054, for the highest versus the lowest intake). No association between dairy consumption and the incidence of diabetes was observed in men.

DATA FROM OBSERVATIONAL STUDIES—ASSOCIATION BETWEEN DIETARY PATTERNS THAT INCLUDE DAIRY PRODUCTS AND TYPE 2 DIABETES

Although cohort studies that investigate the relationship between the intake of dairy products and the incidence of T2D usually make adjustments for different variables such as the age of the participants, total energy intake, or BMI, they fail to take into account the effect of multiple, concurrent dietary exposures (Hoffmann et al., 2004; Nettleton et al., 2008). A possible way to consider the combined effect of food intakes on the development of a disease is the use of dietary patterns. Table 6 summarizes several of the recent prospective cohort studies that have investigated the relationship between dietary patterns and the risk of T2D. Even if clear conclusions on the specific effects of dairy foods per se on the incidence of diabetes are harder to draw with dietary pattern-based studies, overall an inverse relationship has been observed between the incidence of T2D and dietary patterns characterized by high intake in low-fat dairy products, whole grain, fruit, and vegetables (Nettleton et al., 2008).

In a recent cohort study, Erber et al. (2010) investigated the effects of three dietary patterns, "Fat and Meat," "Vegetables," and "Fruit and Milk" on the risk of diabetes in 75,512 Caucasians, Japanese American, and native Hawaiians of the Multiethnic Cohort (MEC). The "Fruit and milk" pattern, including food groups such as milk, yogurt, cheese, citrus fruits, melons, and berries, was found to lower the risk of diabetes in women (HR = 0.85; 95% CI 0.76–0.96; P_{trend} 0.005), whereas the beneficial effect was less pronounced in men (HR = 0.92; 95% CI 0.83–1.02; P_{trend} 0.04). Similarly, Villegas et al. (2010), who prospectively examined the association between dietary patterns and the incidence of T2D in 64,191 middle-aged women (40–70 years) from the Shanghai Women's Health Study, found that the participants presenting the highest intake of dairy milk and the lowest intake of staple foods had a lower risk of T2D, with a RR of 0.78 (95% CI 0.71–0.86) compared to participants

Table 6 Observational studies on the association between dietary patterns that include dairy products and type 2 diabetes

Study	Number, nationality, and gender of subjects	Location	Design of the Cohort (follow-up, years)	Dietary patterns[1]	Results	Adjustments
Brunner et al., 2008	7,731 men and women	London	Whitehall II study (15 years)	"Unhealthy" (white bread, processed meat, fries, full-cream milk), "Sweet" (white bread, biscuits, cakes, processed meat, high-fat dairy products), "Mediterranean-like" (fruit, vegetables, rice, pasta, wine), "Healthy" (fruit, vegetables, whole-meal bread, low-fat dairy, little alcohol)	"Healthy" versus "Unhealthy" pattern: HR = 0.74, 95% CI 0.58–0.94, P_{trend} 0.016	Age, sex, total energy, smoking, physical activity, social class, ethnicity
Nettleton et al., 2008[2]	2,634 men and 2,377 women (2,177 whites, 1,205 blacks, 1,016 Hispanics, and 613 Chinese)	Six study centers in the United States	Multi-Ethnic Study of Atherosclerosis (MESA) (~5 years)	Four PCA-derived dietary patterns ("Fats and Processed Meats," "Vegetables and Fish," "Beans, Tomatoes, and Refined Grains," "Whole Grains and Fruit"), Priori-defined low-risk food pattern score based on the consumption of 10 food groups (i.e., whole grains, nuts/seeds, vegetables, low-fat dairy, coffee, high-fat dairy, red meat, processed meat, white potatoes, regular soda)	"Whole grains and Fruit" pattern: HR = 0.85, 95% CI 0.76–0.95, P_{trend} 0.005 A priori low-risk food pattern: HR = 0.87, 95% CI 0.81–0.99, P_{trend} 0.04	Age, sex, total energy, smoking, physical activity, education level, race/ethnicity, study center, weekly supplement
Liese et al., 2009[3]	862 men and women (346 whites, 516 blacks/Hispanics)	Four study centers in the United States	Insulin Resistance Atherosclerosis Study (IRAS) (5 years)	Eight food groups from the "DASH" diet (i.e., grains, vegetables, fruits, dairy, meat, nuts/seeds/legumes, fats/oils, sweets)	Whites: OR = 0.31, 95% CI 0.13–0.75, P_{trend} 0.03 Blacks/Hispanics: OR = 1.34, 95% CI 0.70–2.58, P_{trend} 0.68	Age, BMI, sex, total energy, smoking, diabetes history, education level, race/ethnicity/clinic, glucose tolerance status
Erber et al., 2010	36,256 men and 39,256 women (29,759 Caucasians, 35,244 Japanese Americans, and 10,509 Native Hawaiians)	Hawaii and California	The Multiethnic Cohort (14 years)	"Fat and Meat" (discretionary fat, meat, eggs, cheese), "Vegetables" (high amounts of vegetables and low loading of fruits), "Fruit and Milk" (high loadings on milk, yogurt, cheese, fruits)	"Fruit and milk" pattern: Women: HR = 0.85, 95% CI 0.76–0.96, P_{trend} 0.005 Men: HR = 0.92, 95% CI 0.83–1.02, P_{trend} 0.04	BMI, total energy, smoking, high blood pressure, alcohol, physical activity, education level, marital status, and stratified by age at cohort entry
Villegas et al., 2010	64,191 Chinese women	Shanghai	Shanghai Women's Health Study (SWHS) (6.9 years)	"Cluster 1" (highest intake of staples, i.e., rice, noodles, steamed bread, bread), "Cluster 2" (highest intake of dairy milk), "Cluster 3" (highest intake of poultry, pork, red meat, fish and shellfish, eggs, fruits and vegetables and the highest energy intake)	"Cluster 2" versus "Cluster 1": RR = 0.78, 95% CI 0.71–0.86	Age, BMI, total energy, smoking, hypertension, alcohol, physical activity, education level, income level, occupation, WHR

RR = relative risk; OR = odds ratio; HR = hazard ratio; BMI = body mass index; WHR = waist-to-hip ratio.
[1]Dietary patterns are characterized by greater loading of the listed food groups. [2]"Fats and Processed Meats" (greater loading for the food groups "fats and oils," "high-fat and processed meats," "fried potatoes," "salty snacks," and "desserts"); "Vegetables and Fish" (greater loading for various vegetable groups [i.e., "dark-yellow," "cruciferous," "other vegetables"], "fish," and "soups"); "Beans, Tomatoes and Refined Grains" (greater loadings for food groups "legumes," "tomatoes," "refined bread, rice, pasta," "high-fat cheeses and cheese and cream sauces," "avocados and guacamole"); "Whole Grains and Fruit" (greater loading for food groups "whole-grain bread, rice, pasta," "fruit," "seeds, nuts, peanut butter," "green leafy vegetables," and "low-fat milk"). [3]Results for tertile 3 versus tertile 1.

presenting the highest intake in staples and the lowest intake in dairy milk.

Moreover, Nettleton et al. (2008) reported that dietary patterns characterized by high intake of whole grains, fruit, nuts/seeds, green leafy vegetables, and low-fat dairy foods (a pattern derived empirically by principal component analysis and referred to as "whole grains and fruit") were associated with a 15% reduction of the risk of T2D (HR = 0.85; 95% CI 0.76–0.95; P_{trend} 0.005) in 5,011 participants from the Multi-Ethnic Study of Atherosclerosis (MESA) including white, black, Hispanic, and Chinese adults aged 45–84 years. An inverse association between the incidence of diabetes and a dietary pattern defined a priori by the authors as "low-risk food pattern," based on the intake of foods previously reported to be associated with T2D, was also observed (HR = 0.87; 95% CI 0.81–0.99; P_{trend} 0.04). On the other hand, dietary patterns presenting a high intake of refined grains, red meat, tomatoes, beans, and high-fat dairy foods were linked to a 18% higher risk of T2D (HR = 1.18; 95% CI 01.06–1.32; P_{trend} 0.004).

A "healthy" eating pattern, characterized by a high intake of fruit, vegetables, whole-meal bread, low-fat dairy, and little alcohol, was reported to reduce the risk of diabetes during 15 years of follow-up in the Whitehall II study ("healthy" versus "unhealthy" patterns; HR = 0.74; 95% CI 0.58–0.94; P_{trend} 0.016) (Brunner et al., 2008). The impact of the adherence to the Dietary Approaches to Stop Hypertension (DASH), a diet rich in fruits, vegetables, and low-fat dairy products, on the risk of T2D has also been investigated by Liese et al. (2009) in 862 black, Hispanic, and non-Hispanic white participants of the Insulin Resistance Atherosclerosis Study (IRAS). An inverse correlation between the adherence to the DASH diet and the incidence of T2D in whites was observed (tertile 3 versus tertile 1; OR = 0.31; 95% CI 0.13–0.75; P_{trend} 0.03), but not in Hispanics or blacks (tertile 3 versus tertile 1; OR = 1.34; 95% CI 0.70–2.58; P_{trend} 0.68). The lack of association in blacks and Hispanics, as pointed out by the authors, could be due to the limited number of participants.

Elwood et al. (2010) performed a meta-analysis of prospective cohort studies investigating the relationship between dairy food consumption and the incidence of T2D. Of the five studies included in the meta-analysis, one study looked at dietary patterns while the other four looked specifically at the intake of dairy products. Individuals with the highest consumption of dairy food, compared to those with the lowest intake, were found to present a lower risk of diabetes (RR = 0.85; 95% CI 0.75–0.96; P for homogeneity 0.122). This finding is in accordance with most of the results from prospective studies that seem to show a consistent inverse relationship between the incidence of T2D and the consumption of dairy foods, particularly low-fat dairy products.

DAIRY CONSUMPTION AND TYPE 2 DIABETES: POSSIBLE MECHANISMS

While the incidence of T2D is greatly influenced by genetic predisposition and lifestyle, dietary composition may play an important role in its development and its complications (Risérus et al., 2009). As presented in the following sections, proteins as well as several non-protein constituents of milk have been suggested to contribute to the beneficial effect of dairy food consumption on the incidence of T2D.

Effects of Non-Protein Constituents in Dairy Products on the Risk of Type 2 Diabetes and Glucose Regulation

Lactose is the second major milk constituent after water (Lindmark Månsson, 2008). However, despite its high content in cow's milk, the current knowledge on the possible roles of dairy components in the incidence of T2D does not seem to suggest lactose as a dominant factor in the inverse association between dairy food consumption and diabetes. In fact, lactose intake was not found to be significantly related to T2D (RR = 0.99; 95% CI 0.80–1.22; P_{trend} 0.33) in a prospective study by Janket et al. (2003), in which the intake of total and specific types of sugar, including lactose, was investigated in 38,480 women of The Women's Heath Study. Lactose, dairy protein, and fat have been suggested to enhance satiety and lower the risk of overweight and obesity, known to be major risk factors for T2D, compared with other high-carbohydrate foods and beverages (Pereira et al., 2002). However, in a study by Pereira et al. (2002), adjusting for these nutrients had no significant effects on the inverse relationship they observed between dairy food intake and the insulin resistance syndrome.

Cow's milk is known to be a major food source of calcium, magnesium, and vitamin D. Vitamin D deficiency has been shown, in animal and human models, to increase peripheral tissue insulin resistance and decrease insulin secretion (Isaia et al., 2001; Moreira and Hamadeh, 2010). In fact, a positive correlation between 25-hydroxyvitamin D (25(OH)D) concentration and insulin sensitivity was observed in glucose-tolerant individuals, whereas hypovitaminosis D was found to have negative effect on pancreatic β-cell function (Chiu et al., 2004). Magnesium deficiency has also been found to have adverse effects on insulin action (Lopez-Ridaura et al., 2004; Martini et al., 2010). Hypomagnesemia may alter tyrosine-kinase activity at the insulin receptor level and may lead to increased intracellular calcium concentration, and these two effects can result in impaired insulin action (Martini et al., 2010). On the other hand, calcium is needed for insulin-mediated intracellular processes and changes in calcium concentration in insulin target tissues may affect the insulin signal transduction and cause peripheral insulin resistance (Pittas et al., 2007).

Although vitamin D, magnesium, and calcium may play a role in glucose regulation, the findings of their effects on the risk of T2D are conflicting and the significance of their possible contribution to the inverse association observed between dairy product intake and diabetes remains unclear. Total vitamin D and total calcium intake were significantly associated with the risk of T2D in a prospective study by Pittas et al. (2006). These associations, however, were found when these nutrients were obtained from supplement, rather than from dietary sources (Pittas et al.,

2006). On the other hand, calcium and vitamin D intake alone were not linked to the risk of T2D in a further study by Kirii et al. (2009), and a positive association between calcium and T2D was observed only in individuals with a higher vitamin D intake. Yet, calcium plus vitamin D supplementation was not shown to reduce the risk of diabetes in a randomized placebo-controlled trial (de Boer et al., 2008). Calcium and vitamin D intake was not found either to explain the inverse association between dairy consumption and the insulin resistance syndrome observed in overweight adults of The Coronary Artery Risk Development in Young Adults (CARDIA) study (Pereira et al., 2002). Vitamin D is mainly produced endogenously by the skin during exposure to the sunlight, and diet only accounts for approximately 30% of the vitamin D obtained (Moreira and Hamadeh, 2010). Thus, dietary intake of this vitamin alone may not provide an accurate indication of an individual's overall vitamin D status.

The impact of dietary fat on the incidence of T2D has been of particular interest due to the role that fatty acids play on glucose regulation by affecting cell membrane function, insulin signaling, genetic expression, and enzymatic activity (Risérus et al., 2009). Several factors may affect bovine milk fatty acid composition, including the breed, the type of feeding, and the season (Pešek et al., 2005; Lindmark Månsson, 2008), but in general bovine milk contains approximately 4.2% of fat, of which almost 70% is saturated whereas monounsaturated and polyunsaturated fatty acids account for about 25 and 2.3%, respectively (Lindmark Månsson, 2008). Moreover, approximately 7–9% of milk fat is composed of medium-chain fatty acids (MCFAs) (Pešek et al., 2005), which present a chain length of 8–12 carbons, and about 3–7% of short-chain fatty acids, which present a chain length of 4–6 carbons (Pešek et al., 2005; Lindmark Månsson, 2008). A diet characterized by a high intake of saturated fat disturbed insulin sensitivity (Pfeuffer and Schrezenmeir, 2006; Wein et al., 2009). On the other hand, MCFAs have been reported to improve insulin sensitivity in some animal and human studies (Pfeuffer and Schrezenmeir, 2002, 2006; Wein et al., 2009). Unlike long-chain fatty acids, MCFAs do not require binding to fatty acid-binding proteins for their transport within cells and across membranes and this distinction impacts numerous regulatory pathways. However, the effect of MCFAs on insulin level or plasma glucose observed in most human or animal studies is not so clear-cut (Pfeuffer and Schrezenmeir, 2006).

Another type of fatty acid naturally found in cow's milk, *trans*-palmitoleic acids, was recently suggested to have a preventive effect on the risk of diabetes (Mozaffarian et al., 2010). Mozaffarian et al. (2010) examined the association between blood *trans*-palmitoleate level and the incidence of T2D in 3,736 subjects of the Cardiovascular Health Study. Higher circulating levels of *trans*-palmitoleate were associated with significantly lower risk of T2D (HR 0.41, 95% CI 0.27–0.64 [quintiles 4 versus quintiles 1] and HR 0.38, 95% CI 0.24–0.62 [quintiles 5 versus quintiles 1]). The authors speculated that *trans*-palmitoleate could partly mimic the biological function of adipose-produced *cis*-palmitoleate that have been found in animal experiments to improve insulin resistance and related metabolic abnormalities in hepatic and skeletal muscle in addition to help in suppressing hepatic fat production. Increased hepatic fat production has been suggested to contribute to nonalcoholic steatohepatitis, a condition associated with insulin resistance (Mozaffarian et al., 2010).

In order to assess the role of specific fatty acids in the pathogenesis of T2D, Krachler et al. (2008) investigated the erythrocyte membrane fatty acid (EMFA) composition, which provides an estimation of the fatty acid intake, of 159 individuals with T2D and 291 referents. Higher levels of pentadecanoic (15:0) and heptadecanoic (17:0) in erythrocyte membrane, which were found to be positively correlated with the intake of high-fat dairy products such as butter and 3% fat milk, were associated with a lower risk of T2D (OR = 0.65; 95% CI 0.50–0.85; P 0.002 and OR = 0.47; 95% CI 0.35–0.63; P <0.001, respectively) (Krachler et al., 2008). Kröger et al. (2011) also reported a strong link between the incidence of T2D and the fatty acid profile of erythrocyte membrane phospholipids and the activity of desaturase enzymes in 2,724 subjects, including 673 diabetes cases, of The European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam Study. However, dietary fatty acid profile was found to present only a modest or low correlation with EMFA composition and to not be significantly related to the risk of diabetes (Kröger et al., 2011).

Although milk fat may have some effects on the incidence of T2D, it seems unlikely that it is the primary mechanism for the inverse association between diabetes and dairy product consumption observed in epidemiological studies, as the protective effect of dairy has been more strongly linked to the intake of low-fat dairy foods. From the mixed results yielded by the studies that have assessed the effects of vitamin D, calcium, and magnesium on the incidence of T2D, it also seems unlikely that these nutrients are the main contributors to the beneficial effect of dairy product consumption on the risk of T2D reported in observational studies. Moreover, even if there are evidences of possible associations between dairy fat, vitamin D, calcium, magnesium and the incidence of T2D, assessing whether the reported effects are specific to the risk of developing diabetes is complex because these components have also been suggested to have antiobesity properties and/or help in lowering the risk of the metabolic syndrome, which are both in turn associated with the risk of developing T2D (Pfeuffer and Schrezenmeir, 2006).

Effects of Milk Casein and Whey Proteins on Glucose Regulation

The possible effect of dairy foods on the incidence of T2D has also been suggested to be attributable to the protein fraction of milk. Dietary proteins are found to cause the release of insulin in both healthy and diabetic individuals when ingested with or without carbohydrate. Moreover, dietary proteins are also known to induce glucagon secretion (Claessens et al., 2008). Milk protein seems to induce an increase in postprandial insulin response with a reduction in postprandial blood

glucose levels (Liljeberg Elmståhl and Björck, 2001; Östman et al., 2001). When compared with casein or other animal or vegetable proteins, whey proteins were found to be particularly insulinotrophic (Nilsson et al., 2004). This finding was suggested to be due to the rapid digestibility of whey proteins (Akhavan et al., 2010) and its high content of branched-chain amino acids (particularly leucine), which are known for their high capacity to increase insulin response (Petersen et al., 2009). Several amino acids can potentially act as direct insulin secretagogues (Nilsson et al., 2007), and increased levels of amino acids in postprandial plasma are believed to be associated with enhanced insulin response (Calbet and MacLean, 2002). Leucine, isoleucine, valine, lysine, and threonine were among the essential amino acids showing a pronounced postprandial increase in plasma following the ingestion of whey drink and were also shown to present the strongest correlation with insulin response (Nilsson et al., 2004).

It has also been suggested that the glycemic regulatory properties of milk protein may be related to its effect on the release of incretin hormones from the gut. In fact, proteins, such as whey protein, trigger the release of cholecystokinin, glucagon-like peptide-1 (GLP-1), glucose-dependent insulinotropic polypeptide (GIP), and peptide tyrosine tyrosine (PYY) from the intestinal enteroendocrine cells (Akhavan et al., 2010). These peptides play an important role in stomach emptying and glycemic control. A protein-stimulated insulin response in healthy individuals or individuals with T2D that did not mirror the increase in plasma amino acid levels was observed in some studies, supporting the role of incretin hormones in protein-stimulated insulin release (Nilsson et al., 2004).

A recent study on the effects of consumption of whey protein (WP) and whey protein hydrolysate (WPH) before a meal on satiety and on blood glucose and insulin concentrations in young adults (Akhavan et al., 2010) showed that only WP contributed to blood glucose regulation by insulin-dependent and insulin-independent mechanisms. This observation suggests that noninsulinotropic mechanisms require stimulation arising from the digestion of intact proteins. Despite the fact that the mechanism of action by which premeal WP leads to postmeal glucose regulation is not well defined, it seems probable that the insulin-independent actions of premeal consumption of WP is partly due to the effect of protein on gastric emptying caused by the release of incretin hormones. A mixture of branched-chain amino acids was shown to produce the same effect as intact whey protein on insulin, but not on gut hormones (Nilsson et al., 2004). This observation, as well as the possible existence of a threshold for amino acid-induced GIP release (Nilsson et al., 2007), may explain the lack of effect of WPH on blood glucose.

Manders et al. (2006) investigated the effects on blood glucose concentration of the consumption of a beverage containing casein protein hydrolysate/leucine mixture after each main meal. They observed a reduction in the prevalence of hyperglycemia, with a significant reduction of the average 24-hour blood glucose level, in T2D patients receiving the protein hydrolysate/leucine mixture compared to those receiving a placebo mixture. Similarly, the addition to a glucose drink of 5–20 g of protein in the form of a protein supplement known as "glycemic index lowering peptide" (GILP), which is composed of a blend of whey peptides and intact whey protein with high content of branched-chain amino acids, was shown to cause a dose-dependent decrease in postprandial glycemia in 10 healthy subjects (Petersen et al., 2009). Although the mechanism by which GILP causes a decrease in the postprandial glycemia is not known, several hypotheses have been raised, such as the effect of branched-chain amino acids in stimulating insulin response, the effect of whey protein on incretin hormone secretion, and the effect of the whey peptide fraction as a source of inhibitors of dipeptidyl peptidase-IV (DPP-IV), a member of the prolyl endopeptidase family known to hydrolyze incretin hormones such as GLP-1 (Petersen et al., 2009). Interestingly, in animal studies showing the effect of whey protein on the reduction of postprandial glycemia, higher levels of intact GIP and GLP-1 were observed, and this despite the fact that only the secretion of GLP-1 was increased (Gunnarsson et al., 2006). It is suggested that the digestion of whey protein might generate protein fragments (di- or tripeptides) that may act as endogenous inhibitors of DPP-IV, and thus lead to decreased degradation of the incretin hormones and to higher levels of intact GIP and GLP-1 (Drucker, 2006; Gunnarsson et al., 2006).

Effect of Protein Intake on the Incidence of T2D—Is the Effect Specific to Dairy Proteins?

Amino acids and dietary proteins are known to play an important role in the modulation of glucose metabolism and insulin sensitivity (Tremblay et al., 2007). In addition to dairy foods, the consumption of several other food products, such as fish (Ouellet et al., 2007; Tremblay et al., 2007; Patel et al., 2009), soy (Lavigne et al., 2000), and nut (Jiang et al., 2002), has also been reported to have an impact on glycemia regulation.

It was observed in a rat study that animals fed with soy proteins and cod proteins present an improved fasting glucose tolerance and insulin sensitivity when compared to rats fed with casein proteins (Lavigne et al., 2000). However, the beneficial effect of soy protein on glycemic control has not always been observed in human studies (Gobert et al., 2010) and differences in postprandial glucose, as well as hormonal responses following the ingestion of dairy and soy proteins, have also not always been observed (Bos et al., 2003).

It is well known that the incidence of T2D in individuals from regions such as Alaska and Greenland, where the consumption of fish is important, is particularly low (Tremblay et al., 2007). The beneficial effect of fish consumption was initially believed to be attributable to the fish oil, but recent studies on the consumption of lean fish, such as cod, have also shown an inverse correlation with the incidence of T2D (Tremblay et al., 2007), suggesting that fish protein might actually be the constituent responsible for the beneficial effect of lean fish consumption. In studies in which animals were administered a high-fat diet,

cod protein-fed rats were shown to be protected against the development of insulin resistance in comparison with rats fed soy or casein protein (Lavigne et al., 2001). The protective effect of cod on insulin resistance is believed to be attributable to an enhanced insulin-stimulated glucose uptake in skeletal muscles (Lavigne et al., 2001).

These data suggest that dairy is not unique, and that it might be the general intake of proteins and amino acids that modulate insulin action and glucose metabolism, and thus have beneficial effects in the prevention of T2D.

CONCLUDING REMARKS

Epidemiological and observational studies have suggested a positive correlation between dairy food intake and the risk of development of T1D in genetically predisposed individuals. However, it should be noted that the correlations or associations shown by ecological or epidemiological studies between cow's milk and T1D do not necessarily indicate a cause and effect relationship. Although several hypotheses have been suggested to explain this relationship, it is not possible to conclude from the actual data available that cow's milk per se is pathogenic in T1D. Several lines of evidence show that the gut-associated immune system is a keystone in the development of autoimmune diseases and that individuals predisposed to T1D may simply present an enhanced autoimmunity to dietary proteins in general and not specifically to dairy protein.

On the other hand, observational studies have also suggested that the consumption of dairy products may reduce the incidence of T2D. While several milk constituents may contribute to the beneficial effect of dairy food intake on lowering the risk of developing T2D, the protein fraction of milk may play a dominant role in the observed effects. However, the exact mechanism by which dairy proteins participate in insulin/glucose regulation is still unclear. The consumption of other dietary proteins, such as fish proteins, has also been shown to be inversely correlated to the development of metabolic syndrome and T2D, suggesting that the effect of protein consumption on T2D might not be uniquely associated with dairy proteins.

More research is required to fully understand the physiological effects of the consumption of dairy products, as well as the role and mechanisms of specific constituents of dairy foods that may be involved in influencing the development of diabetes. However, designing studies that could provide absolute certainty whether dairy product consumption is associated with diabetes is challenging. Intervention studies may be the best approach to obtain clearer answers on the relation between cow's milk consumption and T1D, but breast-feeding remains an important confounding factor that is impossible to completely eliminate as it cannot ethically be limited. On the other hand, nutritional interventions are unlikely to be feasible for adults in which diet is less easy to control and would have to be monitored for decades in order to evaluate the effect of dairy food consumption on the risk of T2D. Finally, although diet can play a role in the incidence of diabetes, it should be kept in mind that it is only one among many other environmental factors, including lifestyle, that may contribute to the development of the disease.

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