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Lower Consumption of Cow Milk Protein A1 β-Casein at 2 Years of Age, Rather than Consumption among 11- to 14-Year-Old Adolescents, May Explain the Lower Incidence of Type 1 Diabetes in Iceland than in Scandinavia

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Key Words
Caseins · Milk proteins · Cow's milk · Dietary research · Type 1 diabetes

Abstract
Aim: To compare the consumption of the cow milk proteins A1 and B β-casein among children and adolescents in Iceland and Scandinavia (Norway, Denmark, Sweden and Finland) as this might explain the lower incidence of type 1 diabetes (per 100,000/year, 0–14 years) in Iceland. ***Methods:*** The consumption of A1 β-casein in each country among 2- and 11- to 14-year-old children was calculated from results on food intake and on cow milk protein concentration. The consumption values were then compared and evaluated against the incidence of type 1 diabetes. ***Results:*** There was a significant difference between the consumption of A1 ($p = 0.034$) as well as the sum of A1 and B ($p = 0.021$) β-casein in Iceland and Scandinavia for 2-year-old children. In the same age group, consumption of A1 β-casein correlated with the incidence of type 1 diabetes in the countries ($r = 0.9$; $p = 0.037$). No significant difference in consumption of A1 or the sum of A1 and B β-casein was found for 11- to 14-year-old adolescents. ***Conclusion:*** This study supports that lower consumption of A1 β-casein might be related to the lower incidence of type 1 diabetes in Iceland than in Scandinavia. Additionally it indicates that consumption in young childhood might be of more importance for the development of the disease incidence than consumption in adolescence.

Introduction

The hypothesis of cow milk diabetogenicity has been supported by affirmative results from studies in some countries but not in others [1–6]. It is possible that this is due to differences in the protein composition of the milk consumed within those countries.

The amount of A1 and B β-casein in Icelandic milk is lower than in milk from the genetically related nations of Scandinavia, i.e. Norway, Denmark, Sweden and Finland, which might explain the lower incidence of type 1 diabetes (per 100,000/year, 0–14 years) in Iceland [1, 7–11]. Furthermore, the increase in incidence in the youngest age group 0–4 years of age seen in the Nordic countries

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Table 1. An overview of the studies used to evaluate the consumption of milk and milk products in Iceland and Scandinavia among 2-year-old children and 11- to 14-year-old adolescents

	2-year-olds			11- to 14-year-olds		
	group (first author)	year of study	dietary method	group (first author)	year of study	dietary method
Iceland	Gunnarsson [18]	1998–1999	3-day weighted dietary record	Steingrimsdottir [23]	1992–1993	24-hour recall and a food frequency questionnaire, amount evaluated
Norway	Hay [19]	1991–1992	7-day weighted dietary record	Frost-Andersen [24]	1993	Food frequency questionnaire, amount evaluated
Denmark	Andersen [20]	1995	7-day estimated dietary record	Andersen [20]	1995	7-day dietary record, amount evaluated
Sweden	Kylberg [21]	1980	7-day weighted dietary record	HULKEN [25]	1989	7-day dietary record, amount evaluated
Finland	Ylönen [22]	1992	3-day estimated dietary record	Räsänen [26]	1980	48-hour recall, amount evaluated

is not seen in Iceland. The difference in incidence cannot be explained by differences in distribution and frequency of the known HLA class II genes [12]. The diabetogenic effect of A1 β-casein is supported by earlier animal studies and studies on antibodies in human [13, 14]. Furthermore, per capita consumption of A1 and B β-casein has been correlated with the incidence of type 1 diabetes in a study involving Iceland and the Scandinavian countries [8] as well as A1 β-casein in a study of 20 countries [15] in an update of the earlier one [8].

Per capita consumption is information from the total sale or supply of food for a whole country, so it does not give information on actual consumption or for different age groups. Type 1 diabetes is mainly diagnosed in childhood and adolescence, therefore an exact measure of the consumption of milk during childhood is needed to evaluate relationships between milk proteins and the etiology of the disease. An increase in incidence of type 1 diabetes is seen worldwide [9]. Because cow's milk is so widely used, and is an important source of nutrients, particularly in children, more knowledge about constituents of cow's milk that could potentially make it diabetogenic is urgently needed. It is also of great importance to investigate the association of the diet in young childhood and adolescence with type 1 diabetes [16, 17].

The aim of the present study was to compare the consumption of the cow milk proteins A1 and B β-casein among children and adolescents in Iceland and Scandinavia as this might partly explain the lower incidence of type 1 diabetes in Iceland.

Methods

Dietary Research

Dietary studies on children 0–14 years in Iceland, Norway, Denmark, Sweden and Finland were evaluated to find comparable studies performed in young childhood and adolescence. The studies used for information about dietary intake were thoroughly evaluated and had to fulfill certain criteria to qualify for the present study, i.e., participants randomly chosen and at least 30 children involved, comparable age of the participants and the dietary method used had to include recording of an amount of food consumed. Dietary surveys on 2-year-old children and 11- to 14-year-old adolescents were found to fulfill the criteria set for the present study and to be the only studies performed so far in all five countries to give comparable data for diets at a certain age in childhood (table 1) [18–26].

Information regarding the amount of milk and milk products consumed was found in the selected scientific papers and by contact with authors. The method of processing is similar between the Nordic countries and milk, soured milk, cream, ice cream and yoghourt from each country was found to have similar amount of milk protein. Furthermore, the proportional consumption pattern of the varying products in the age groups was alike. Cheese was calculated separately due to its much higher content of protein, which is essentially all casein protein, but consumption of cheese at 2 years of age was almost identical in the Nordic countries. The small amount of milk proteins found in biscuits and cakes, processed fish and meat products, chocolate as well as soups and sauces was also considered but the percentage of milk protein from these sources was found to be small. This source was omitted from the analysis as it was of minor importance as a source of milk protein, and as recording of these products, in the selected studies, varied more than for milk products and its inclusion in the data would therefore increase inaccuracy.

Table 2. Figures for A1 β-casein and the sum of A1 and B β-casein in milk from the Nordic countries from two different sources, and the incidence of type 1 diabetes in the Nordic countries

	A1 β-casein (8)[1]	A1 β-casein (1)[1]	A1 and B β-casein (8)[1]	A1 and B β-casein (1)[1]	Incidence of type 1 diabetes
Iceland	25.0	35.6	25.0	38.4	9
Norway	46.0	40.8	47.8	46.1	21
Denmark	49.2	41.0	58.6	54.5	22
Sweden	46.3	43.7	47.1	48.3	25
Finland	51.0	42.7	51.1	46.1	30

[1] Figures are given as percentages of total β-casein.

Concentration of A1 and B β-Casein in Milk

Available sources for β-casein composition of cow's milk were used to calculate the amount of A1 and B β-casein in milk. The data of Elliott et al. [8] estimated β-casein A1 and B contents in milk over a number of years (early 1990s) using data on the genetic composition of the breeds in the different countries, as well as from chemical analysis of milk. The other source of A1 and B β-casein data was from our previous study [1], and involved the chemical analysis of the amount of these proteins in consumer packages of cow's milk from the largest consumption areas in Iceland and Scandinavia. All samples were taken at similar time points in autumn and spring in all the countries and all samples were analyzed using the same analytical method (late 1990s). The contents of A1 and B β-casein were fairly constant between seasons over a 2-year period for a particular country [1]. The range from both studies represents the total concentration range for A1 and B β-casein concentration in milk over the period the consumption data was collected. The A1 and B β-casein levels in Icelandic milk in both studies were always lower than those found in the four Scandinavian countries [1, 8]. Table 2 shows the fraction of A1 and the sum of A1 and B β-casein fractions in milk [1, 8] demonstrating the much lower contribution of B β-casein. It also tabulates the incidence of type 1 diabetes (per 100,000/year, 0–14 years) in the five countries [9, 10] used in the correlation. These are mainly from the beginning of 1990, which was found to be appropriate in comparison with the dietary studies.

Calculation of Consumption

Consumption was calculated from mean intake and the percentage of milk proteins in the milk and the different milk products as well as the total percentage of β-casein and the percentages of A1 and B β-casein of total β-casein. The formula for the calculation of the consumption of A1 β-casein was:

$$A1_{cons} = C \times p \times b \times A1_{prop}$$

where $A1_{cons}$ = consumption of A1 (g), C = mean amount of milk or milk product consumed (g), p = proportion of milk protein in the product, b = proportion of total β-casein of total protein, and $A1_{prop}$ = proportion of A1 of total β-casein.

The amount of B β-casein was calculated using the same method, but this variant is found in much lower amount in milk.

Statistical Analysis

Incidence of type 1 diabetes in Iceland and the other Nordic countries are from collective papers stating comparable figures to the 1990s [9, 10]. To evaluate the relationship between the average consumption of A1, and the sum of A1 and B, β-casein in each country and the incidence of type 1 diabetes in the countries, the Spearman correlation was used. As the Spearman correlation is a rank test, the possibility that the low incidence in Iceland is regarded as an outlier is not possible. The Mann-Whitney test was used to evaluate the differences between the consumption of A1, and the sum of A1 and B, β-casein in Iceland vs. Scandinavia (four vs. eight values for each of the β-caseins' concentration in milk, calculated averages based on all analysis of cow's milk from different areas and references [1, 8]).

Table 3. Calculated consumption of A1 β-casein among 2-year-old children as well as 11- to 14-year-old boys and girls in Nordic countries

	A1 β-casein mean consumption		
	2-year-old children, g/day	11- to 14-year-old boys, g/day	11- to 14-year-old girls, g/day
Iceland	1.7	3.7	2.8
Norway	2.0	4.9	3.6
Denmark	2.7	3.7	3.0
Sweden	2.1	4.8	3.7
Finland	2.8	4.7	3.5

Results

Consumption of milk in the different countries varied in all the groups, with 2-year-olds in Denmark consuming the highest amount, while Icelanders consumed the highest amount at 11–14 years [18–26]. Table 3 shows the mean consumption of A1 β-casein in the age groups, calculated from results on intake of milk and milk products and from the average concentration of A1 β-casein in those milk products. Among 2-year-olds the Icelandic consumption figure is the lowest, both when using the lowest or highest figures for A1 β-casein in milk from Ice-

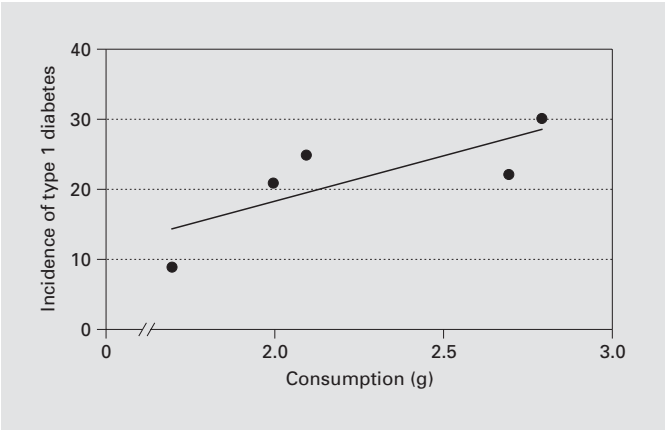

Fig. 1. Correlation between the calculated consumption of A1 β-casein among 2-year-old children in the Nordic countries and the incidence of type 1 diabetes (per 100,000/year, 0–14 years) ($r = 0.9$; $p = 0.037$).

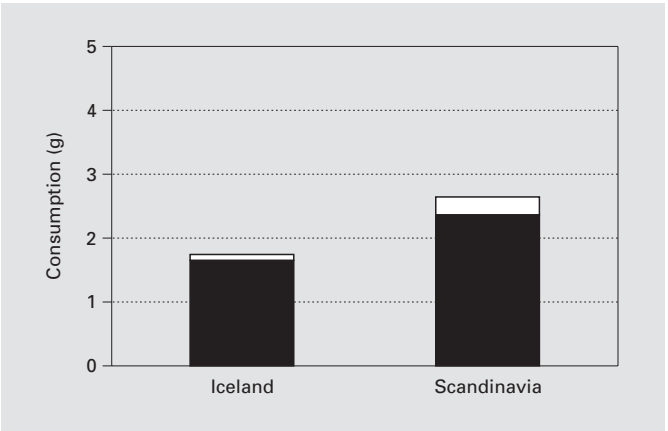

Fig. 2. Calculated consumption of A1 (■) and B (□) β-casein among 2-year-old children in Iceland and Scandinavia (g/day) ($p < 0.05$).

land for calculation. The consumption of A1 β-casein among 2-year-olds correlated with the incidence of type 1 diabetes (per 100,000/year, 0–14 years) in the five countries ($r = 0.9$; $p = 0.037$) (fig. 1). The correlation with the sum of A1 and B β-casein was not significant ($p = 0.188$). No correlation was found for 11- to 14-year-olds, with either boys or girls ($p > 0.05$).

There was a significant difference in the consumption of A1 β-casein among 2-year-olds between Iceland and Scandinavia ($p = 0.034$) and the same was true for the sum of A1 and B β-casein ($p = 0.021$) (fig. 2). A significant difference was not found in the 11- to 14-year-old age group, neither among boys ($p = 0.332$ for A1 β-casein and $p = 0.115$ for the sum of A1 and B β-casein) nor girls ($p = 0.182$ for A1 β-casein and $p = 0.055$ for the sum of A1 and B β-casein), but the consumption figure for Iceland was lower than in Scandinavia (fig. 3).

Discussion

The significant difference in the consumption of A1 and B β-casein among 2-year-old children, and correlation between the consumption and the incidence of type 1 diabetes (per 100,000/year, 0–14 years) in the different countries supports that these proteins might be important factors in the development of type 1 diabetes. Furthermore, the difference in type 1 diabetes between Iceland and the Nordic countries in the age group 0–4 years is even higher, supporting the findings. The current results

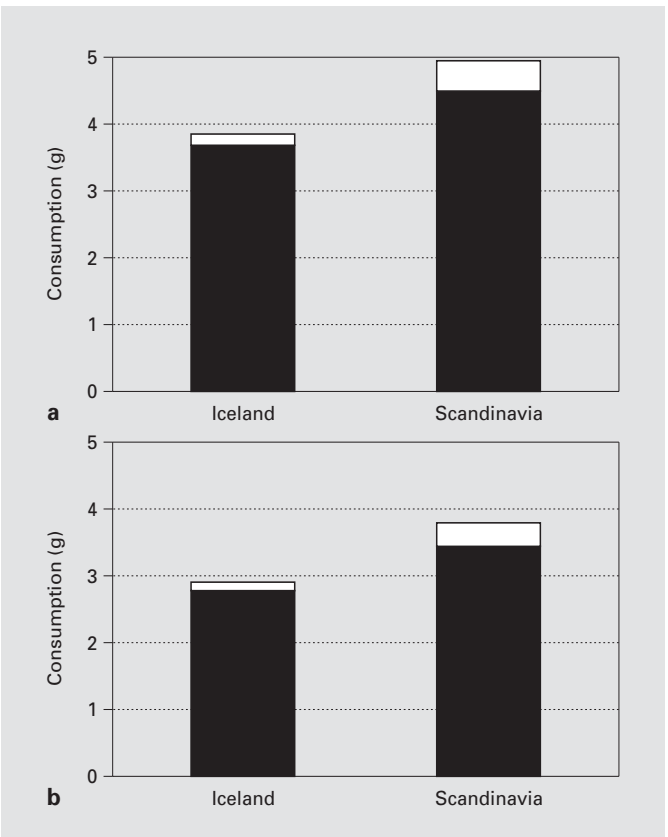

Fig. 3. Calculated consumption of A1 (■) and B (□) β-casein among 11- to 14-year-old boys (**a**) and girls (**b**) in Iceland and Scandinavia (g/day) ($p > 0.05$).

indicate that the consumption of milk early in life might be of more importance than the consumption of milk later in life for development of type 1 diabetes. However, although not significant, the mean amount consumed among 11- to 14-year-old children was also lower in Iceland.

The two dominant variants of the cow milk protein β-casein are the A1 and A2 variants, with the β-casein B variant being found at much lower frequency. A1 β-casein has been shown to be diabetogenic in experimental animals and B β-casein has been suggested to act in a similar way [8, 13] although a later similar study did not fully support the former results [27]. β-Casein A1 and B have chemical similarities and have been proposed to release upon digestion a diabetogenic factor, β-casomorphine-7 [8, 13, 28], which affects the immune system, but the mechanism is not clear. The peptide can form in the digestive tract and is absorbed and found in the blood of for example small beagles but not adult dogs [29]. A2 β-casein does not release this bioactive protein fraction upon digestion [8, 28]. Furthermore, elevated levels of antibodies to A1 β-casein have been demonstrated in patients with newly diagnosed type 1 diabetes [14] and a strong correlation was found between per capita consumption of A1, as well as the sum of A1 and B, β-casein and the incidence of type 1 diabetes in an epidemiological ten country study including Iceland and the four Scandinavian countries [8]. This study explores further the proposed relationship between consumption of A1 β-casein and incidence of type 1 diabetes and adds to earlier results as it finds a relationship between the consumption of children and the disease. However, neither this study nor other epidemiological studies can rule out the possibility that it is the A2 protein that is protective against type 1 diabetes as this is always high when A1 is low. This has not been studied. The reason for less association between the incidence of type 1 diabetes and the sum of A1 and B β-casein than with A1 alone in the present study might be the relatively large variation in the available figures for B β-casein and that it is only found in measurable amounts in some breeds of cattle [7]. Another recent ecological study including 20 countries found per capita consumption of A1 β-casein to be related to type 1 diabetes but did not find B β-casein to be significantly correlated to the disease [15]. A1 β-casein is thus more stable and must always have more impact as a potential diabetogenic factor as its amount in milk is many times higher.

The development of type 1 diabetes occurs in genetically predisposed individuals. The inhabitants of the Nordic countries are genetically related [11]. Furthermore, studies on the distribution and frequency of the known HLA class II genes in Iceland and Norway showed that they cannot explain the difference in incidence between the countries [12]. However, the Finnish population has a special genetic susceptibility to type 1 diabetes [30, 31].

The theory that the consumption of cow's milk and cow's milk products is related to type 1 diabetes has long been known and debated. Studies have been inconsistent [1–6] and the relationship seems therefore to exist in some countries and not in others, indicating that the cow's milk itself might contain different amounts of diabetogenic factors in different countries. Icelanders consume large amounts of milk products while the incidence of type 1 diabetes is low. It was therefore important to determine the amount of the milk proteins A1 and B β-casein consumed by Icelandic youths, compared to Scandinavian youths, as type 1 diabetes around the world often develops before or around puberty. Previous studies have shown that the per capita consumption of A1, as well as the sum of A1 and B, β-casein is low in Iceland [8].

In general, studies have often focused on the early exposure to cow's milk, as it is the first major source of foreign proteins to which infants are exposed. It has been shown that bottle-fed infants are much more likely to have antibody response to bovine β-casein than breast-fed infants [32]. An earlier case-control study showed that within the Icelandic population, cow milk consumption in infancy was not related to type 1 diabetes in Iceland [1] while this has been seen in other countries with higher incidence of type 1 diabetes, such as Finland [5]. The present study shows a lower consumption of A1 and B β-casein among young children in Iceland than in Scandinavia and indicates that differences in the consumption of A1 β-casein among young children may explain the varying incidence of type 1 diabetes in the countries. The fact that the type 1 diabetes population in Iceland is older than in the other Nordic countries due to very few children diagnosed in the age group 0–4 years supports the findings. The observed difference of somewhat lower consumption of A1 and B β-casein among 11- to 14-year-old adolescents in Iceland compared to Scandinavia were not significant. It might be that exposure throughout life until the disease comes forward is of importance [6, 16, 33–36] but it is clear that the vulnerability to proteins and peptides is greatest over the first months of life.

The findings demonstrate that cow's milk varies in its diabetogenicity which may be because of the milk's β-casein composition. Other milk proteins such as bovine serum albumin and β-lactoglobulin have been suggested to be diabetogenic, but the evidence is currently strongest for the β-casein variants [37, 38]. The findings also add to former studies by indicating that the consumption in young childhood may be more important than consumption later in life for the development of type 1 diabetes. The study can however not exclude the potential diabetogenic effects of A1 or B β-casein among adolescents. The methods of the dietary studies used for comparison among the 11- to 14-year-old children were not all prospective recordings as was the case for the 2-year-old children. All of them though included amount of milk or milk products consumed. Although the dietary studies for the 2-year-old children range over almost 20 years, it does not seem that the milk consumption in this age group has changed very much over this period. For example, in 1984 in the study by Kylberg et al. [21] the mean intake of cow's milk was 300 ml, and in a study in 1999 by Bramhagen and Axelsson [39] on 2-year-olds, this figure was found to be 290 ml. However, as there was no other information on intake of milk products in this study, it could not be included in the calculations on A1 β-casein consumption. Incidence figures used in the correlation are mainly from the beginning of 1990, which was found to be the appropriate in comparison with the dietary studies.

Icelandic cattle have been isolated from interbreeding with other cattle breeds for over 1,100 years, resulting in a lower frequency of genes coding for A1 and B β-casein in Icelandic cattle which is related to the old Scandinavian breed [7]. However, interbreeding within and between countries has been and still is a common practice in Scandinavia [40]. This explains the marked difference in the frequency of β-casein variants in Iceland when compared with Scandinavia or other developed countries. It is likely that over relatively long periods, or decades, cattle breeding programs have resulted in some variations in β-casein fraction. This has for example been seen in Finland where the A1 β-casein allele is more frequent in milking cows in Finland in 1997 compared to 1965 [41]. The amount of β-casein variants in the milk from all the countries used in this study is likely to have changed over the years. We therefore found it suitable to use the whole possible range of β-casein variant concentration that has been analyzed in the literature, over the time period of the dietary studies, in our calculations. Casein variants are less affected by feeding of the herd than are whey proteins, but it cannot be excluded that differences in feeding of the herds partly explain the difference in β-casein variants between the countries. However, the Icelandic consumers' milk clearly always has the lowest amount of A1 and B β-casein compared to milk from Scandinavia.

Further studies, such as clinical trials, are needed to examine further the importance of the association seen between milk proteins and type 1 diabetes, and milk is not likely to be the only factor involved in the etiology of the disease. However, an ecologic study like this is an important link as it supports the possibility of causation earlier seen in experimental studies [13]. As milk is an important source of nutrients, especially for young children, it may later be preferable to develop milk that is devoid of possible diabetogenic proteins by changing the protein composition.

This study supports that lower consumption of A1 β-casein is related to the lower incidence of type 1 diabetes in Iceland than in Scandinavia. Additionally it indicates that consumption in young childhood might be of more importance for the development of the disease incidence than consumption in adolescence.

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