The Case for Elimination of Cow's Milk in Early Infancy in the Prevention of Type 1 Diabetes: The Finnish Experience

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I. INTRODUCTION

A central element in the aetiopathogenesis of type 1 diabetes is the specific destruction of the pancreatic β-cells due to a cellular/humoral autoimmune process in genetically predisposed subjects in response to an external triggering factor.[1,2] Dietary factors have been consistently listed as possible triggers, but only a few systematic studies have been carried out in this field. Amongst the various dietary risk factors proposed, such as cow milk (CM) proteins, nitrosamines, and plant proteins, the first mentioned appear to be the most likely candidate, deserving a closer look in the light of studies in both animals and man.

The overall objective of the intervention trial described below is to study whether complete avoidance of CM exposure during at least the first 6 months of life prevents type 1 diabetes in genetically susceptible children. This approach is based on convincing animal experiments indicating that CM proteins may be a common trigger of the autoimmune process leading to type 1 diabetes. We and others have also presented evidence in man that these dietary proteins may be implicated in the aetiopathogenesis of type 1 diabetes in children. The findings from both types of study very strongly justify the intervention study under consideration, the implications of which may prove far-reaching.

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II. EVIDENCE IN SUPPORT OF THE ROLE OF COW MILK PROTEINS IN THE AETIOLOGY AND PATHOGENESIS OF TYPE 1 DIABETES

Evidence for the role of proteins in CM in the pathogenesis of type 1 diabetes may be roughly divided into three categories:

(a) data from experimental animals;
(b) epidemiological and ecological evidence; and
(c) immune response to the protein fractions in CM in patients with type 1 diabetes.

A. Experiments in Animals

Experiments in BioBreeding (BB) rats and non-obese diabetic (NOD) mice have clearly

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demonstrated the deleterious effect of CM proteins on pancreatic β-cells. Prompted by anecdotal reports suggesting a low incidence of type 1 diabetes in people from countries with a low protein intake, with emergence of the disease on adopting a high protein intake, Elliott and Martin[3] were the first to report that manipulation of the protein component in the diet of BB rats affects their natural history of diabetes: feeding rats a semi-synthetic amino acid diet from the onset of weaning led to a substantial reduction in the incidence of diabetes, from 52% in rats receiving CM protein supplementation to 15%. Subsequent studies by the Toronto group confirmed that the effect of CM proteins is established during a relatively narrow, early phase in the postnatal (weaning) period.[4] The prevention of diabetes by a synthetic diet in which protein was replaced by a purified casein hydrolysate before weaning has subsequently been confirmed in the NOD mouse.[5,6]

Casein is not a likely diabetes trigger in BB rats, since the incidence of diabetes is reduced or completely eliminated when a semi-synthetic diet is supplemented with 25% casein as the only protein source.[7,8] In the NOD mouse, however, a diet containing casein as the sole source of protein produced diabetes when the dietary experiment was started from just before weaning and whey protein not.[5,9] The same diet in which casein was totally hydrolysed did not cause diabetes.[9,10]

However, in spite of similarities to human type 1 diabetes, animal models have several important differences compared with the human situation.

B. Observations in Man

During the past 10 years, several epidemiological studies have provided strong evidence for the role of CM in the pathogenesis of type 1 diabetes. This information may be divided into three categories, namely, ecological, time series, and case–control studies. The first paper published by Borch-Johnsen *et al.* in 1984[11] focused on the change of the incidence of type 1 diabetes in parts of Norway and Sweden and its association with the change in breast feeding (BF) frequency. They found a peak in the incidence of type 1 diabetes about 9 years after the period in which the BF frequency was at its lowest. They also reported that the BF time had been shorter in type 1 diabetes patients than in controls.

Scott[12] found that there was a close association between the total consumption of CM and the incidence of type 1 diabetes in children. The correlation coefficient was 0.86. Dahl-Jørgensen *et al.*[13] showed that the association was even stronger, with a correlation coefficient of 0.96, when more reliable data from carefully validated registries were used (Diabetes Epidemiology Research International Study Group, 12 countries).

1. *Role of BF and Early Exposure to CM*

Since the primary report of Borch-Johnsen *et al.*[11] on the inverse association between BF and the risk of type 1 diabetes, several studies in various countries have confirmed the association, although in a few studies no association (e.g., ref. 14) was observed. Some of the studies were population-based case–control studies, of which the largest are described below.

Blom *et al.*[15] reported in 1989 on BF findings from a Swedish nationwide case–referent study, comprising 339 newly diagnosed children with type 1 diabetes and 527 referent children, matched according to age, sex, and county. When the children were divided into two age groups, 0–6 and 7–14 years respectively, the referent children in the former had a significantly longer duration of BF than the diabetic children. As regards the introduction of artificial feeding, no significant differences were found between diabetic and referent children in any age group.[15] When dividing the same subjects into three age groups, 0–4, 5–9, and 10–14 years, a multivariate analysis indicated a BF duration of less than 3 months to be a significant risk determinant for type 1 diabetes in the youngest age group, 0–4 years.[16] In the same study population, Dahlquist *et al.*[17] concluded that an early, i.e., before 4 months of age, exposure to CM formula is related to an increased risk for early-onset type 1 diabetes.

In our population-based "Childhood Diabetes in Finland" (DiMe) study, the data on feeding in infancy comprised questions on the duration of overall and exclusive BF, the age at introduction of supplementary milk feeding and solid foods to the diet, and the type of supplementary milk feeding. The duration of exclusive BF and the age at the start of supplementary CM feeding were both related to diabetes risk: comparing 103 0 to 6-year-old diabetic children to birth-date and sex-matched controls randomly selected from the Finnish population registry, type 1 diabetes patients had been more often breast-fed for less than 6 months overall and exclusively breast-fed

for less than 2–3 months. A greater proportion of diabetic compared with control children had received supplementary CM by the age of 1, 2, or 3 months. The effects of the infant feeding on the risk of type 1 diabetes remained significant after adjusting for the mother's education.[18] We have subsequently confirmed this in a larger series of 426 pairs of 7 to 14-year-old subjects in the same project[19]: the risk of type 1 diabetes was decreased in the children who were totally or exclusively breast-fed for at least 2 or 3 months. Those children who were younger than 3 months at the time when supplementary milk feeding was initiated had an increased risk for type 1 diabetes. Furthermore, the adjustment for mother's age, education, child's birth weight, or birth order did not affect the results.[19]

It may be argued that the associations between the mode of infant feeding and the occurrence of type 1 diabetes are due to the protective role of BF. Breast milk compensates for the deficiency of the local immunoglobulin production of the gut during early infancy and protects the infant from gastrointestinal infections. On the other hand, early supplementation of foreign proteins, e.g., CM proteins, may lead to increased absorption of dietary antigens as the gut in early infancy is more permeable than later. This problem was addressed in the recent study of Virtanen *et al.*,[20] where both the length of exclusive BF and the time of the start of supplementary feeding were tested as variables in a logistic regression model for the risk of type 1 diabetes. In that study, the whole "Childhood Diabetes in Finland" series of incident cases less than 15 years of age, in which dietary data and controls were available, was analysed. The controls comprised subjects included in the previously published studies on 0 to 6-year-olds[18] and 7 to 14-year-olds,[19] and in addition 0 to 6-year-old controls whose data were not obtained in the first control series. Altogether, 690 case–control pairs were formed. The independent effects of overall BF and the age at introduction of dairy products were studied by introducing each of them as three dichotomous variables (2–3 months/other, 4–5 months/other, ≥6 months/other) to the logistic regression model. When both the duration of exclusive BF and the age at introduction of dairy products were introduced to the logistic regression model, only the age at introduction of dairy products was significant. The association between the age at introduction of dairy products and risk for type 1 diabetes did not differ by birth year cohort.[20] As the age at introduction of dairy products and the duration of BF are highly intercorrelated, they should be adjusted to each other when studying the independent effects of each on the risk of type 1 diabetes. This was done in the study described above, the largest population studied to date,[20] and the result underlines the impact of CM supplementation in early infancy as a dietary risk factor of type 1 diabetes.

A detailed description of the various BF studies in the context of type 1 diabetes is presented in a review article on putative environmental factors in the aetiology of type 1 diabetes.[21]

Gerstein[22] has recently presented a critical review and summary of the studies on BF and type 1 diabetes. In an analysis of 13 case–control studies published in 15 papers, he considered six methodological variables and performed meta-analysis of four of the studies fulfilling at least five of the six criteria. In this meta-analysis he estimated that the overall odds ratio for type 1 diabetes in patients having had a shorter duration of BF than 3 months was 1.43 with a 95% confidence interval of 1.15–1.77, and the overall odds ratio for the risk of type 1 diabetes in children exposed to CM before the age of 3 months was 1.63 with a 95% confidence interval of 1.22–2.17. According to these calculations, the incidence of type 1 diabetes could be reduced by at least 30% if CM was eliminated from the diet during the first 3 months of life.

Case–control studies probably underestimate the risk caused by an early exposure to CM. Many of the controls do not have a genetic risk of developing type 1 diabetes and therefore it does not matter whether they are exposed to CM early. This was demonstrated in the study of Kostraba *et al.*,[23] where it was shown that when genetically high-risk individuals (homozygous for non-ASP in position 57 in the HLA-DQB chain) exposed to CM before the age of 3 months were compared with low-risk individuals unexposed to CM before the age of 3 months, the odds ratio for the risk of type 1 diabetes was 11.3, the small number of individuals making the confidence interval (1.2–102) quite large, however. Another confounding factor is that many studies consider the total length of BF, while most likely only exclusive BF offers sufficient protection from CM proteins.

2. Immune Response to CM Proteins in Newly Diagnosed Type 1 Diabetics

We reported in 1988[24] that children with newly diagnosed type 1 diabetes had significantly higher levels of serum IgA antibodies to CM and BLG, and IgG antibodies to BLG than age-matched controls. In diabetic children with a duration of the disease exceeding 5 years, the levels of CM and BLG antibodies did not differ from those of the controls. The CM and BLG antibodies were measured by an enzyme-linked immunosorbent assay (ELISA). We inferred that either the pattern of CM consumption is altered in children who become diabetic, or the immunological reactivity to proteins in CM is enhanced, or the permeability of their intestines to CM proteins is increased.[24] This finding has been recently confirmed in our large, nationwide "Childhood Diabetes in Finland" study, comprising 706 children with newly diagnosed type 1 diabetes, 456 non-diabetic siblings, and 105 unrelated age-matched controls below 7 years of age.[25] The median level of IgG antibodies to CM in the youngest patients with newly diagnosed type 1 diabetes (under the age of 3 years) was seven times and that of IgA antibodies more than six times higher than that of the unrelated controls in the same age range. The youngest patients had the highest levels of IgG antibodies both to CM and to BLG. The median level of IgG antibodies to BLG was significantly higher in patients than in controls in the youngest group of patients (<3 years), but also when compared with siblings in the age group 7–14.9 years. We inferred that a high titre of CM antibodies reflects an insult and immunization caused by CM proteins, which in some genetically susceptible individuals may lead to type 1 diabetes after a long but variable time interval.[25]

Dahlquist *et al.*[17] reported from the Swedish nationwide case–referent study that most CM antibody levels tended to be increased among diabetic compared with control children, the difference being significant for IgA antibodies to CM and BLG. The differences in these antibodies were more pronounced among children with an early clinical onset of type 1 diabetes. In a multiple logistic regression analysis, they observed that IgA class BLG antibodies were significantly associated with an increased risk of diabetes at a young age independent of islet cell antibody status and of an early weaning to CM formula. The authors concluded that in genetically susceptible children early exposure to BLG might be one trigger of the autoimmune process leading to the development of type 1 diabetes.[17]

Studies by the Toronto group have provided evidence for a diabetogenic role of bovine serum albumin (BSA), specifically a short 17-amino acid fragment (amino acids 152–168, "ABBOS") in the core region of the molecule.[26,27] In this context, it is of interest that newly diagnosed type 1 diabetic children had elevated serum concentrations of IgG anti-BSA antibodies, the bulk of which were specific for ABBOS, measured by particle concentration fluorescence immunoassay (PCFIA). IgA antibodies were elevated as well, but not IgM antibodies. The antibody concentrations declined after diagnosis, reaching normal levels in most patients within 1–2 years. Much lower serum concentrations of anti-BSA antibodies were found in all control subjects, and only 2.5% of them had small amounts of ABBOS-specific IgG.[28]

3. What is the Mechanism of the Deleterious Effect of CM Proteins on the Pancreatic β-Cells?

(a) The BSA hypothesis

Based mainly on work in the BB rat, but also on observations in man,[28] the Toronto group has proposed a central role for BSA and the ABBOS fragment in the pathogenesis of type 1 diabetes.[27,29] They observed the presence of circulating IgG antibodies to BSA and BLG in the BB rat. The levels of anti-BSA antibodies prior to the diagnosis of diabetes were inversely related to age at manifestation of the disease.[27] Another group has reported similar findings of elevated levels of antibodies to BSA in the diabetic NOD mouse compared with non-diabetic mice, indicative of an exaggerated immune response to BSA.[30] We have also recently measured anti-BSA antibodies with the ELISA technique in the "Childhood Diabetes in Finland" project in a large number of newly diagnosed diabetic children, their siblings, and other controls. Patients had significantly higher titres of IgG and IgA class antibodies to BSA than those of the comparison groups of all ages, but also in these antibodies the difference was greatest in the youngest age group, below 3 years of age.[31]

In the comparison between the amino acid sequences of human serum albumin and BSA, the Toronto group was able to identify a portion of BSA between amino acids 138 and 166 as the region where most divergence from the human

sequence occurs. The region (amino acids 157–175) also demonstrates the greatest sequence difference between rat serum albumin and BSA. It was also found that antibodies to BSA cross-react with a β-cell membrane protein of M_r 69 000 which is induced in islets by γ-interferon stimulation.[26] This protein, p69, has now been cloned through screening an islet library with BSA antibodies (Dosch H-M, personal communication). An identical protein was recently cloned by the Boston group using sera from prediabetic subjects, and it appeared to show sequence homology with BSA.[32] These experiments were important in demonstrating at the molecular level the possible mechanism by which individuals exposed to a foreign protein present in CM develop antibodies that recognize through molecular mimicry a particular protein present in the islet β-cell membrane. This may indicate an ongoing autoimmune process leading to β-cell destruction and type 1 diabetes.[27]

The BSA hypothesis can thus be summarized as follows: both in humans and in spontaneously diabetic animals the ingestion of CM in the neonatal period or early in infancy results in the entry of bovine milk proteins into the circulation, due to the incomplete barrier function of the gastrointestinal tract. It should also be borne in mind that infants may also be exposed to CM proteins through the maternal diet as a result of transfer of dietary antigens into breast milk.[33] BSA exposure leads to immunological sensitization (both T-cell generation and antibody production). Any subsequent viral infection which generates systemic interferon levels and thus induces transient p69 expression (which structurally resembles BSA) in the β-cells exposes them transiently to immune-mediated destruction.

The timing of exposure is one central feature of the BSA hypothesis. Exposure needs to occur during a relatively narrow "window" of vulnerability to establish the immune response against BSA. It is well established that the gut is permeable to proteins during the first 2–3 months in infancy.[34,35] This time period is very similar to the age by which CM supplementation has appeared as a dietary risk factor of type 1 diabetes, as mentioned earlier. Determinants of the above-mentioned "window" could include age-dependent changes in gut permeability to macromolecules such as CM proteins, maturation of specific gut proteases, and of gut-based tolerance mechanisms to foreign proteins. The gut permeability to proteins may also later in infancy be increased temporarily due to diarrhoea: the circulating levels of egg albumin after an oral load of the protein are higher in infants recovering from acute diarrhoea than in controls.[36] Holm *et al.* studied the intestinal absorption of the macromolecule human α-lactalbumin during and after an episode of acute gastroenteritis in young children (median age 12 months), and found the absorption to be significantly higher 5–8 weeks later compared with the acute phase and with that of the reference children.[37]

(b) The casein fragment hypothesis

A casein-containing diet causes diabetes in NOD mice,[5,9] and partial enzymatic hydrolysates retain the diabetogenic activity.[10] The hydrophobic casein peptides in question are capable of stimulating human macrophages,[38] and similar peptides have been demonstrated in the blood of humans after CM ingestion.[39] Such casein peptides could act as an "adjuvant" to macrophages involved in the killing of β-cells in prediabetic individuals.[10]

(c) Other possible mechanisms

There may still be other mechanisms involved. For example, Issa-Chergui *et al.*[8] proposed in their study in diabetes-prone rats that a compound produced when milk proteins are heated in the presence of sugars may play a role in altering patterns of disease. They noted that dietary constituents are heated to high temperatures during pelleting of rat chow and defatted milk is subjected to variable periods of heating during the production of skim milk powders.[8] Evidently, the various procedures used in the production of CM-based infant formula and the possible changes in these procedures over time are a most interesting focus for evaluation in the context of the hypothesis on the role of CM proteins in the evolution of type 1 diabetes.

If either of the hypothetical models presented above [(a), (b)] were correct, the development of type 1 diabetes could be prevented through strict avoidance of exposure to dietary CM proteins during the vulnerable, postnatal period identified in relevant rodent models[27] and by BF studies in humans, and supported by our current knowledge of the slow maturation of the intestinal immunological barrier against dietary macromolecules during this phase.

III. BRIEF DESCRIPTION OF A DIETARY INTERVENTION TRIAL

Although the exact mechanism(s) by which CM proteins affect pancreatic β-cells in young (high-risk) infants, remain(s) to be verified, we consider the indirect evidence from animal experiments and observations in man, particularly the risk linked with early supplementation of CM proteins reviewed briefly above, to be sufficient to justify a dietary intervention trial.[40] The formula to be used, a casein hydrolysate, fulfils the criteria outlined earlier for avoiding dietary CM proteins. It does not contain either BSA or large peptide fragments, and it does not cause diabetes in the NOD mouse.[10] We have planned an intervention trial to study whether the primary prevention of type 1 diabetes is possible in high-risk individuals by avoiding CM proteins during the first 6–8 months of life.

A. Subjects

Newborn infants from families with a first-degree relative with type 1 diabetes will be recruited to the study.

1. Recruitment

Pregnant type 1 diabetic mothers will be identified via hospitals monitoring them. Type 1 diabetic fathers will be identified by available history or data already in record as well as through interviews of mothers at (pre-) delivery maternity clinic visits. Type 1 diabetic siblings will be identified through various diabetes clinics.

2. Participating Hospitals and Recruitment Projection

Thirteen major hospitals in Finland have expressed their willingness to participate, covering approximately 70% of the population. Based on the results of previous studies in Finland, it is estimated that approximately 250–300 genetically high-risk newborns per year can be recruited via these units. To shorten the recruitment period, discussions are underway with investigators from major population centres in Sweden, Norway, and Estonia to join the study. Fifteen Canadian hospitals have agreed to participate, and discussions are underway with some major U.S. centres to consider joining the study.

3. Sample Size

The sample size was originally calculated for Finland based on the prevalence of type 1 diabetes in fathers and mothers of probands in the DiMe-study,[41] and the conversion rate in non-diabetic siblings in the same study.[42] Based on these studies, it appeared that in Finland the 10-year risk of type 1 diabetes for newborns with an affected parent or sibling is approximately 4%. The risk in the other North European countries and in North America is likely to be somewhat lower, and therefore in the power calculation a conservative estimate of the frequency of type 1 diabetes by age 10 years for the control group (receiving CM products after weaning) has been set at 3%.

The rationale behind genetic prescreening would be a maximal reduction in the number of subjects to be treated and followed, while retaining the necessary number of potential diabetics in the study and control groups. Neonatal screening for high-risk HLA-DQ genes will be undertaken, and only infants with a high risk (about 10%) of developing type 1 diabetes by the age of 10 years will be followed. The sample size was calculated based on the estimation that the risk of type 1 diabetes will be reduced by at least 40% by the age of 10 years. To get a significant result we need 2000 high-risk infants for the study, and in order to identify these, 6000 newborn infants have to be screened.

B. Dietary Manipulation

Infant feeding practices will be altered as little as possible by the trial. In particular, BF practice(s) will be entirely at the discretion of participating mothers. However, all relevant data will be recorded. Compliance with the withdrawal of CM will be monitored by assessing formula usage, regular interviews with participating families, and by the appropriate serology.

1. Trial Structure

The trial will be an international, multicentre, double-blind, randomized, controlled study of two different nutritional supplements. After exclusive BF, the infants receive either the test formula, a casein hydrolysate documented to be CM/beef-free (= Diet A), or a CM-based formula (= Diet B). Both groups receive later additions of solid foods listed as CM/beef-free. The test formula

(Diet A) and the control formula (Diet B) are similar in taste and smell. These formulas and CM, beef-free semi-solids and solids will be the only ones used whenever supplementary feeding (i.e., in addition to BF) is required, or at the time of weaning from BF. Dietary supervision will cease 6–8 months after birth. Both formulas are nutritionally equivalent, and will be coded and randomly distributed free of charge.

The epidemiological and experimental studies suggest that the first 2–3 months of life play a central role in sensitization to food proteins; later in life, the normal intestine probably does not allow enough antigenic material to permeate to initiate an immune response. We have chosen the relatively long study period to allow even those infants on long exclusive BF, common in the Nordic countries, to be exposed to study formulas. Post-trial nutrition will follow the accepted practices in the respective country.

C. Genetic and Immunological Studies

1. Genetic Markers

DNA will be extracted from cord blood specimen and HLA-DQ genotype will be defined using DNA hybridization methods.[43] It is essential that the definition of genetic markers to be studied will be agreed upon by the various tissue typing laboratories.

2. Immunological Markers

The following immunological variables will be studied from each sample/child:

(a) islet-cell autoantibodies (ICA), GAD65 antibodies.
(b) CM antibodies (IgG, IgM and IgA, IgE), BLG antibodies (IgG and IgA), and BSA antibodies (IgG, IgM and IgA, IgE).
(c) T-cell reactivity to CM proteins is studied in larger centres with lymphocyte proliferation tests.

The purpose is to collect additional venous blood samples at ages 2, 4, 6, 8, and 10 years, for studies of the above variables.

D. Outcome Assessment

The primary outcome will be the percentage of subjects in each group who develop type 1 diabetes by the age of 10 years, as well as the age of diabetes occurrence. The classification of diabetes is undertaken according to WHO criteria. The non-diabetic subjects will be screened for diabetes by either a fasting or random plasma glucose, as well as a glycated haemoglobin measurement at each biannual follow-up visit, or, if one or both of these are abnormal, by an oral glucose tolerance test to determine diabetes status.

The statistical methods to analyse outcome comprise (a) computing survival curves using a life-table method, subsequently compared by the Mantel–Haenszel chi-square method; and (b) comparing the proportion of diabetics in each group after 10 years by the Mantel–Haenszel chi-square or Fisher exact test.

E. Pilot Study

To establish and test the trial infrastructure, randomization, and food distribution, a pilot study was started in August 1992 including the newborns of 20 type 1 diabetic mothers in Helsinki. Ethical approval had been granted by relevant authorities.

1. Goals

The goals to be analysed in the pilot study are:

(a) trial logistics (flexibility, testing of nutritional questionnaires, co-ordination, food identification, coding, and distribution techniques);
(b) human factors (food acceptance, compliance, collaboration of family, and study team); and
(c) child health and growth, including listing of vaccinations and infections.

2. Course of the Study

The 20th newborn joined the pilot study in February 1993, and thus we will have the series completed by November 1993 (9 months duration of dietary manipulation). Only two out of 22 type 1 diabetic mothers have refused to join the study at the Department of Obstetrics, University of Helsinki, the participation rate being 91%. The infants and their mothers visit the outpatient clinic of the Children's Hospital, University of Helsinki at 3, 6, and 9 months; in addition, the

dietary advisor maintains phone contact with the mother. It has been noted that the mothers have expressed the need for extensive discussion at the maternity ward. When the mother visits the outpatient clinic with the baby, approximately half an hour each is needed for the nurse co-ordinator, dietary advisor, and physician. To date, the advice of the dietary advisor together with other written instructions for the family have functioned well the final evaluation being done after the completion of the pilot study. The instruction booklets containing information for mothers on baby nutrition, as well as the case report forms, are being tested in the ongoing pilot study in Helsinki. Only one mother discontinued participation before the end of the study period.

Despite the long BF period practised in general by mothers in Finland, several mothers have had a short BF period in our pilot study. This is in agreement with the clinical experience of Finnish obstetricians, and with the results in a recent study from the U.S. in which the median days postpartum for women with type 1 diabetes to discontinue BF was 22 days and for control women 52 days.[44]

IV. CONCLUSION

The consequences and costs of type 1 diabetes presenting in childhood are immense, not only in economic and societal terms, but also with regard to human life. Microvascular complications develop over the course of time in a considerable proportion of the patients, with consequent effects on their quality of life. Those individuals manifesting type 1 diabetes in childhood and adolescence may have a several-fold increased risk of macrovascular complications in adult life. It is therefore not difficult to envisage the benefits corresponding to prevention of type 1 diabetes, even if only in some of the cases. The economic burden of type 1 diabetes is admittedly difficult to assess, the costs being composed of three elements: direct, indirect, and psychological.[45] However, it has been assessed that the life-time cost of an individual contracting type 1 diabetes in childhood may reach 1 million U.S. dollars. Thus, it is evident that the high incidence of type 1 diabetes in countries like Finland not only carries a great social impact, but also a heavy economic impact. The significance of the present study is also emphasized by the fact that it is, to our knowledge, the first primary prevention study of type 1 diabetes. It is of interest to note the recent increasing attention by the WHO in early nutrition in the context of the aetiopathogenesis of type 1 diabetes,[46] and it has recently been proposed that research should respond with a new focus on early events.[47]

An External Monitoring Committee will act as a qualified peer review committee not associated with the trial, according to the position statement of the American Diabetes Association *ad hoc* expert committee.[48]

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