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ARTICLE

The Trial to Reduce IDDM in the Genetically at Risk (TRIGR) study: recruitment, intervention and follow-up

The TRIGR Study Group

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Abstract
Aims/hypothesis The Trial to Reduce IDDM in the Genetically at Risk (TRIGR) study was designed to establish whether weaning to a highly hydrolysed formula in infancy subsequently reduces the risk of type 1 diabetes.
Methods The study population comprises newborn infants who have first-degree relatives with type 1 diabetes and meet the increased risk HLA inclusion, but not exclusion criteria. The study is being performed in 15 countries in three continents. First-degree relatives of patients with type 1 diabetes were identified from diabetes clinics, diabetes registries, and from other endocrinology or obstetrics offices and websites. HLA typing was performed at birth from cord or heel stick blood, and the results sent to the study's Data Management Unit within 2 weeks for communication of eligibility to the clinical study centre. All mothers recruited were encouraged to breastfeed. The intervention lasted for 6 to 8 months, and weaning formulas based on hydrolysed casein and standard cow's milk were compared.
Results TRIGR recruited 5,606 infants, of whom 2,160 were enrolled as eligible participants, 6% more than the target of 2,032. Of those enrolled, 80% were exposed to the study formula. The overall retention rate over the first 5 years is 87%, with protocol compliance at 94%. The randomisation code will be opened when the last recruited child turns 10 years of age, i.e. in 2017.
Conclusions/interpretation The TRIGR experience demonstrates the feasibility and successful implementation of an international dietary intervention study. TRIGR is the first ever primary prevention trial for type 1 diabetes and, if completed successfully, will provide a definite answer to the research question.

Trial registration ClinicalTrials.gov NCT00179777
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Keywords First-degree relatives with type 1 diabetes · HLA-typing · Hydrolysed casein · International dietary intervention study · Newborn infants · Protocol compliance · Standard cows' milk · Weaning formulas

Abbreviations

DIPP	Diabetes Prediction and Prevention Study
DMU	Data Management Unit
DSMB	Data Safety and Monitoring Board
ICC	International Coordinating Center
IRB	Institutional Review Board
TRIGR	Trial to Reduce IDDM in the Genetically at Risk

Introduction

The Trial to Reduce IDDM in the Genetically at Risk (TRIGR) study is an international randomised double-blind controlled intervention trial that was designed to establish whether weaning to a highly hydrolysed formula in infancy reduces the risk of type 1 diabetes later in childhood [1, 2]. This report describes completion of recruitment, the intervention and current follow-up status.

The specific TRIGR aims are: (1) to determine whether weaning to a formula comprised of hydrolysed protein, compared with a standard intact foreign cow's milk protein formula, reduces the cumulative incidence of diabetes-predictive autoantibodies and/or clinical diabetes over the first 6 years of life; and (2) to assess whether weaning to the hydrolysate reduces the cumulative incidence of type 1 diabetes in these participants by 10 years of age. The novelty of this approach is that it represents the first-ever appropriately powered primary prevention trial for type 1 diabetes and that it is being implemented across several continents.

Methods

Participants and study design The study design has previously been described in detail [1, 2]. In brief, the TRIGR study population comprises newborn infants who have first-degree relatives with type 1 diabetes (i.e. mother, father or sibling) and who meet the HLA inclusion but none of the exclusion criteria. Blood for analysis of HLA genotypes was collected and sent to the continental central laboratory within 8 days of birth and results sent to the Data Management Unit (DMU) within 2 weeks of age for assessment and confirmation of eligibility, which were then forwarded electronically to the participating centres. This international, double-blinded, prospective, placebo-controlled intervention trial comprises 77 centres (or sites) in 15 countries on three continents (Table 1). Enrolment began on 1 May 2002 and ended on 6 February 2007. Each site obtained appropriate approval from an Ethical Committee or Institutional Review Board (IRB). For details of TRIGR investigators and staff members, see Electronic supplementary material (ESM) Tables 1 and 2.

Recruitment and randomisation First-degree relatives of patients with type 1 diabetes were identified from a variety of sources, including: (1) existing diabetes registries; (2) parents of patients attending paediatric diabetes clinics; (3) prospective parents attending obstetric clinics prior to delivery; (4) prospective parents attending diabetes clinics; (5) local and national advertising; and (6) diabetes societies. In some countries the presence of type 1 diabetes in a mother or father was identified only at the time of birth and appropriate consent was obtained at that time; otherwise consent was obtained during pregnancy. When we first started, there were 11 participating countries with one or more sites each with IRB approval. Within 6 months, the number of enrolling centres grew to 45 (final number 77). Because of the recruitment success, the enrolment target was exceeded by 6% to 2,160. Due to demographics, 2,076 (96 %) of the randomised participants included were white.

The children were randomly assigned to the two treatment groups in a 1:1 ratio using randomly permuted blocks [1]. Randomisation was balanced within each participating centre/country. Web-based randomisation procedures were implemented efficiently. Babies were assigned one of four colour-coded, blinded formulas, two of which contained the hydrolysed test formula, two the control formula. The randomisation code was known only to the manufacturer and the Principal Investigator of the DMU, under supervision of the Data Safety and Monitoring Board (DSMB).

Sample size and power The following background factors were considered when planning the sample size: expected rates of background breastfeeding; non-adherence to the intervention (in 16–17% of participants the intervention was non-existent or shorter than 2 months in the second pilot study [3]); losses to follow-up; and HLA ineligibility.

The sample size and power calculations have been described in detail earlier [1].

More recent updates from the Diabetes Auto Immunity Study in the Young (DAISY), Untersuchungen bei Kindern von Müttern mit Typ-1-Diabetes (BABYDIAB-Study) and Diabetes Prediction and Prevention Study (DIPP) confirm the frequencies of autoantibodies used in our sample size estimate [4–6]. In the DIPP study, 188 young children with

Table 1 Achieved rates of recruitment, enrolment, HLA eligibility (%) and numbers of lost to follow-up participants and non-participants by country

Country	Recruitment (*n*)	Enrolment (*n*)	Eligibility (%)	Lost to follow-up[a]	Not participating[a]
Australia	298	103	39.9		8
Canada	1,423	531	42.2	17	50
Czech Republic	412	164	40.3		10
Estonia	98	35	42.2		3
Finland	1,037	424	45.5		43
Germany	287	112	41.3	1	14
Hungary	66	23	36.5	2	4
Italy	149	54	42.5	1	15
Luxembourg	14	7	50.0		
Netherlands	136	51	40.2		1
Poland	250	95	42.6		33
Spain	133	60	47.2		9
Sweden	209	97	51.6		13
Switzerland	26	13	52.0		2
USA	1,068	391	43.5	14	44
Total	5,606	2,160	43.2	35	249

[a] 31 May 2010

a family member affected by the disease and HLA-conferred disease susceptibility were observed up to the average age of 3 years. Among them, 15 (8%) seroconverted to persistent positivity for at least two of the following autoantibodies: islet cell antibodies, insulin autoantibodies, GAD antibodies and islet antigen 2 antibodies [6].

Assuming a linear increase over the next 3 years, 16% can be expected to test persistently positive for at least two autoantibodies by the age of 6 years. The cumulative incidence of persistent positivity for at least two antibodies was 12.5% by the age of 6 years in the TRIGR pilot study [3].

The projected sample size of 2,032 infants to be randomised for the trial is based on the following assumptions: (1) a confidence level of 95%; (2) a statistical power of 80%; (3) a reduction of 40% in the hazard rate of type 1 diabetes in the intervention group; (4) a dropout rate of 20%; and (5) a frequency of 10% of exclusive breastfeeding up to the age of 6 months. In our study protocol we estimated that the 6 year endpoint based on positivity for two or more autoantibodies would require a sample size of 1,334 children [2].

HLA typing Cord blood was obtained whenever possible, but if unobtainable, a heel stick blood sample was collected on filter paper and immediately sent to the Turku (Europe and Australia) or Pittsburgh (North America) laboratories for HLA genotyping. HLA genotyping for the selected *DQB1* and *DQA1* alleles was performed using sequence-specific oligonucleotide hybridisation, with quality control between the two laboratories carefully maintained. The following genotypes were regarded as eligible: (1) *HLA-DQB1*02/DQB1*0302*; (2) *HLA-DQB1*0302/x* (*x* not *DQB1*02*, *DQB1*0301* or *DQB1*0602*); (3). *HLA-DQA1*05-DQB1*02/y* (*y* not *DQA1*0201-DQB1*02*, *DQB1*0301*, *DQB1*0602* or *DQB1*0603*); (4) *HLA-DQA1*03-DQB1*02/y* (*y* not *DQA1*0201-DQB1*02*, *DQB1*0301*, *DQB1*0602* or *DQB1*0603*).

Parents of ineligible infants were informed that genetic screening suggested no increased susceptibility to type 1 diabetes in their child(ren) and were thanked for their participation. It was emphasised that their child could still develop diabetes despite not meeting the eligibility criteria. The acceptability of this strategy was evident from the fact that many families volunteered for screening of a second child born after the ineligible infant [2].

Study materials A team of TRIGR investigators, as well as staff of the International Coordinating Centre (ICC) and the Nutritional Epidemiology Unit in collaboration with the DMU in Tampa, FL, USA, prepared the Manual of Operations and the various forms. While the official trial language was English, forms and dietary advice leaflets were double-translated into 11 languages and adapted to national practices. It took only 6 months to create the website, develop forms and the Manual of Operations, and to train staff around the world. The Manual of Operations is available to TRIGR Study Group Members.

Intervention Whenever supplementary milk feeding was needed during the intervention period, participants received either the test formula based on extensively hydrolysed casein (Nutramigen; Mead Johnson Nutrition, Evansville, IN, USA) or a control formula created by the company for this study and made with intact (80%, wt/wt) and hydrolysed (20%, wt/wt) milk protein to mask the taste and smell

differences between the two formulas. All recruited mothers were encouraged to breastfeed their infants. The study formulas and the implementation of intervention have been described earlier [1].

Exclusive breastfeeding was defined as absence of any food other than breast milk (banked or mother's), supplementary vitamins or minerals, or water.

The study formulas were packed in four different colours, two for test formula and two for control formula, aiding the blinding process and also providing a hard control for randomisation during data analysis [1]. Import of the coded study formulas to different countries required a major effort to overcome barriers such as customs and storage regulations.

Follow-up during and after intervention Clinical assessment, interviews and blood sampling were performed at the ages of 3, 6, 9, 12, 18 and 24 months (at a study centre or a home visit), and will continue annually until 10 years of age or until manifestation of type 1 diabetes as outlined below. Clinical data at each visit (e.g. weight, height, adverse events, infections etc.) are recorded and transmitted electronically to the DMU. Cow's milk antibodies (IgG and IgA) [7] and α-casein antibodies (IgG and IgA) [8] were measured within 2 months of sampling up to the 9-month visit for use as markers of efficacy of and compliance with the intervention, while other laboratory tests are scheduled in batches. A heparin blood sample is obtained at each sampling time. These samples are sent fresh to the core laboratories in Helsinki and Toronto for isolation of mononuclear cells for mechanistic studies of T cell responses. Local measurements of random plasma glucose and glycosylated haemoglobin are performed at each visit from 12 months onwards and reported to the DMU. The specimen for plasma glucose is preferentially obtained 1 to 2 h postprandially. In the presence of hyperglycaemia or elevated glycosylated haemoglobin, an OGTT is recommended to exclude or confirm diagnosis of diabetes. An OGTT is performed in all non-diabetic participants at the age of 6 and 10 years. If the first OGTT meets WHO criteria for diagnosis of diabetes [9], a second confirmatory test is performed to verify the diagnosis.

The success of the study depends on at least 80% of the children being retained in follow-up to the age of 10 years, with compliance with blood draws (HLA and antibody samples). Strategies successfully implemented in this respect include frequent family phone contacts, newsletters, distribution of TRIGR calendars with reminders and incentives such as birthday cards, study centre parties, websites and active assistance with surveillance of the health of the participating child. The DMU has developed an automated reminder system that repeatedly notifies each centre electronically when each of its participants is due for a visit, and monitors compliance regularly.

Results

Recruitment and randomisation TRIGR recruited 5606 infants, of whom 5001 were randomised (Fig. 1). In the 605 participants (10.8 % of those recruited) not randomised, non-randomisation was mainly due to preterm births (41%) and families changing their minds about participation. The study enrolled 2,160 participants, 6% above the target of 2,032 eligible participants achieved in less than 5 years. The recruitment and eligibility data are presented by country in

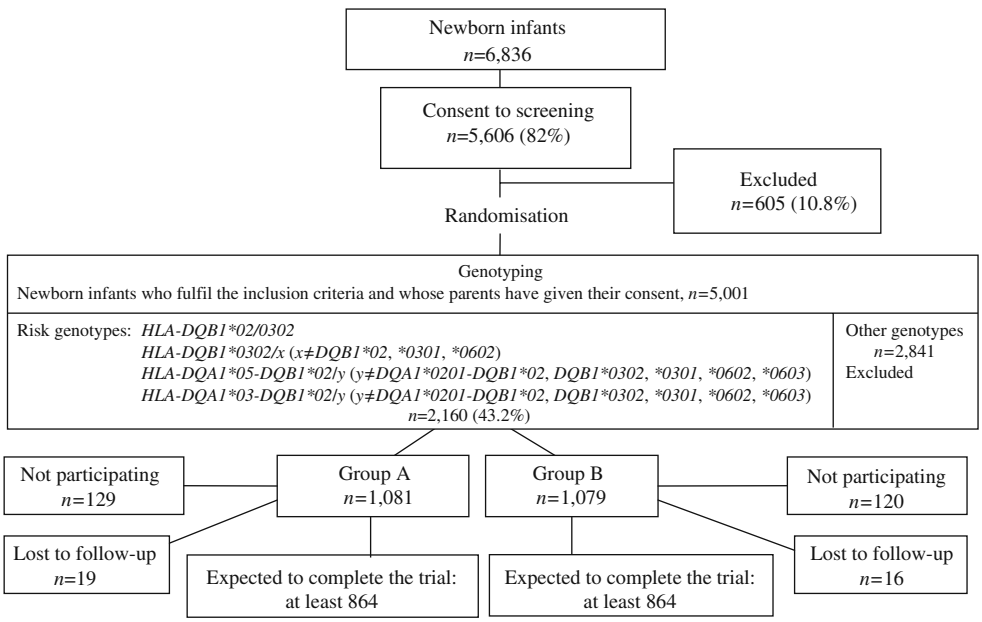

Fig. 1 Trial profile for the participants in TRIGR study

Table 1, which shows that the countries with the highest recruitment and enrolment were Canada, Finland and the USA. For data analyses, countries were grouped by region (Table 2).

Dropouts The dropouts belong to one of the following two categories: (1) non-participants, i.e. participants/families that do not wish to participate further in study interviews and/or testing; or (2) those lost to follow-up, i.e. participants/families lost to follow-up because the family cannot be located, does not respond to study centre inquiries or in any other way refuses all contacts concerning TRIGR.

The number of dropouts is presented by country in Table 1.

Diabetes in the family A breakdown of the diabetic relatives of trial participants by country is presented in ESM Table 3. Mothers with type 1 diabetes were the most common, reflecting recruitment strategies and effectiveness. Finland was an exception, with fathers being the most frequent first-degree relatives (53 %).

HLA eligibility The HLA eligibility percentages are shown by country in Table 1. There were no significant differences in the proportion of HLA-eligible participants between various regions or countries. However, there was a highly significant ($p<0.0001$) heterogeneity in the distribution of the three major eligible HLA genotype groups. The frequencies in European countries (grouped into northern, central and southern Europe), and in Australia, Canada and the USA are presented in Table 2. The differences were mainly due to the higher proportion of the *DQA1*05-DQB1*02* haplotype in southern Europe, whereas *DQB1*0302*-positive haplotypes were more common in northern Europe (Table 2). The distribution in Australia was quite close to that in southern European, whereas the haplotype frequencies in Canada, USA and central Europe were similar.

Dietary compliance Dietary compliance was excellent. Exposure to the Study Formula was 80% exposure, with a 3.6% rate of exclusive breastfeeding until the age 6 months (lower than the predicted frequency of 10%). Exposure to non-recommended formulas during the first 3 days of life was only 3.5%, with cumulative exposure to non-recommended foods among all the participants reaching 16.3% by the end of the intervention. Study Formula intolerance was suspected in 5.7% of the participating infants. These results are well within the range specified by the study design. Breast-feeding rates were high in the present study population. Thus 86.9% of mothers with type 1 diabetes and 93.9% of mothers without type 1 diabetes started to breastfeed, with 51.2% and 70.8%, respectively, continuing to breastfeed when the child was 6 months old.

Antibodies to cow's milk proteins Analysis of cow's milk antibodies from sera collected as part of the study visits between the age of 3 and 9 months substantiates the self-reported dietary and study formula intake collected as part of the study visits between the age of 3 and 9 months. The results are consistent with the reported dietary consumption of food products containing cow's milk or its derivative, with median values near zero before cow's milk introduction and rising significantly thereafter. Because of continued blinding, data by intervention group have not been released.

Overall study retention Currently 86.9% of the original participants are actively participating in the study. The lost

Table 2 Eligible genotypes by European regions, Australia, Canada and the USA

Region	HLA-DQ genotype								
	*DQB1*02/DQ B1*0302*		*DQB1*0302/x*		*DQA1*05-DQB1*02/y*		*DQA1*03-DQB1*02/y*		All
	n	%	*n*	%	*n*	%	*n*	%	*n*
Northern Europe[a]	103	18.5	309	55.6	144	25.9	0	0.0	556
Central Europe[b]	116	25.0	210	45.1	135	29.0	4	0.9	465
Southern Europe[c]	33	29.0	36	31.6	44	38.6	1	0.9	114
Australia	24	23.3	35	34.0	44	42.7	0	0.0	103
Canada	144	27.1	196	36.9	182	34.3	9	1.7	531
USA	96	24.6	167	42.7	120	30.7	8	2.1	391
Total	516	23.9	953	44.1	669	31.0	22	1.0	2,160

Values are *n* (%); χ^2 test=67.791, *df*=15, $p<0.0001$

[a] Northern Europe: Estonia, Finland and Sweden; [b] Central Europe: Czech Republic, Germany, Hungary, Luxembourg, the Netherlands, Poland and Switzerland; [c] Southern Europe: Italy including Sardinia and Spain

to follow-up rates are low (1.6%), but 11.5% are currently not participating. Data presented by country are shown in Table 1. North America had a higher proportion of children lost to follow-up (3.3% vs 0.3%; $p<0.001$) and a lower proportion of non-participating children (9.9% vs 12.5%; $p=0.06$) than Europe and Australia.

Comparison of non-participators with those still active in the study showed no significant differences in HLA risk group, relationship to proband or region. The non-participation rate was highest at the beginning of the study and declined thereafter.

The success of the study so far could be due, at least partly, to the long-lasting collaboration of the investigators and their good relations with staff at the clinical and other sites.

Adverse events All adverse events were reported electronically using on-line event monitoring systems developed and supported by the DMU. Serious events were also reported to the local IRB (according to local guidelines) and the study Chair's office. All adverse events, including those categorised as serious, were reviewed at each DSMB meeting. There have been no concerns regarding safety issues and the study intervention to date. Growth data are routinely monitored by the DSMB. No differences in growth data (participant height, weight and BMI) by treatment arm have been observed to date.

Discussion

The TRIGR Study successfully demonstrates the viability of a properly powered international intervention trial aimed at primary prevention of type 1 diabetes. Some major accomplishments of the study include: (1) development of an infrastructure-intensive clinical trial network tightly linked to the secure, web-based, interactive DMU, thus enabling accurate tracking of the study's rapidly growing blood sample repositories; (2) satisfactory recruitment rate, which improved after an initial delay, with accruals exceeding target rates for most of the final 3 years of accrual; and (3) study-wide protocol compliance (measuring visits, questionnaires and blood samples) 94%, adjusted for dropouts (as of 31 May, 2010). The high level of quality control is due to the combined efforts of the DMU staff, European monitors, North American coordinators, the ICC and the Nutritional Epidemiology Unit staff. In addition, the participant retention rate remains strong, at 87% after 5 years (80% planned). The intervention phase was successfully completed in mid-2007. Compliance with the intervention resulted in all planning variables being met or exceeded. Thus compliance with filling in and returning of forms, and thereby with study centre visits currently exceeds 96%, whereas the expected rate was set at more than 80%.

Compliance with the intervention was meticulously implemented, monitored and recorded. This was accomplished by ongoing training at every level, coordinated regionally using electronic, telephone and face to face formats, with initial bi-annual and then annual Principal Investigator, study nurse and dietitian meetings. The experience gained during the second TRIGR pilot study [3] was invaluable in the development of all protocols and training procedures. Close interaction among study investigators, nurses and research participants was assured, thanks to continuous liaison. Complementary to the international and national websites, TRIGR Newsletters and TRIGR Nutrition Newsletters containing relevant information on the study progress have been distributed to TRIGR staff members and families.

The role of the DMU was central in providing ongoing training to sites and ensuring participation in regularly scheduled conference calls with study coordinators/monitors. The production of daily recruitment reports and monthly compliance reports has provided constant feedback and encouraged the clinical sites to continuously monitor and improve their own performance in the study.

HLA eligibility ranged from 36.5% (Hungary) to 52.0% (Switzerland) and was, on average, very similar in Europe and North America (Table 1). The total rate of 43.2% was only slightly lower than the expected 45.0%, and we compensated for the difference by enrolling somewhat more participants than originally planned. Offspring of affected fathers have about a twofold higher risk of developing type 1 diabetes than offspring of affected mothers [10, 11]. From that point of view it would be preferable to recruit offspring of affected fathers for intervention trials aimed at prevention of clinical disease, as the frequency of clinical endpoints would be higher. However, in most countries it is more difficult to identify prospective fathers with type 1 diabetes than it is to identify pregnant women (i.e. prospective mothers) with the disease. In the TRIGR cohort, the proportion of fathers with type 1 diabetes was on average 34%, ranging from 8.7% in Hungary to 53.4% in Finland, possibly reflecting differences in the structure and function of these countries' healthcare systems.

The first endpoint of TRIGR, i.e. positivity for two or more type 1 diabetes-associated autoantibodies and/or clinical diabetes by the age of 6 years, will be reached in

early 2013, when the youngest recruited participant turns 6 years. Autoantibody results are sent to the families after the 6-year visit. The Study Protocol states that the OGTT tests are done in all children at the ages of 6 and 10 years. The study group has concluded that autoantibody-positive participants cannot be denied participation in any secondary prevention study. On the other hand, most such study protocols tend to exclude individuals who have participated in any earlier prevention trial. The primary and final endpoint of TRIGR, i.e. clinical diabetes by the age of 10 years, will be reached early in 2017. The randomisation codes will be opened when the last recruited child reaches the age of 10 years, i.e. in 2017.

There are two possible scenarios in terms of the trial outcome. If the intervention works and significantly reduces the cumulative incidence of type 1 diabetes by the age of 10 years, this would imply that infants at increased risk of type 1 diabetes should be weaned to a highly hydrolysed formula. If the intervention has no effect, the study recommendation would state that weaning to a highly hydrolysed formula does not decrease the risk of type 1 diabetes, and accordingly such formulas do not provide any benefits to infants carrying increased genetic susceptibility to the disease. The international TRIGR study is powered to provide a definite answer to the controversial question of whether weaning to a hydrolysed formula protects against initiation and progression of type 1 diabetes. This is the first-ever primary prevention trial for type 1 diabetes. If the main hypothesis of the study is proven to be correct, primary prevention of at least some cases of type 1 diabetes and reduction of the associated morbidity and mortality rates, and healthcare costs could become a realistic goal. This seemingly innocuous strategy could be applied to the general population with increased genetic risk, from which some 90% of new cases of type 1 diabetes are derived [12].

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Duality of interest The authors declare that there is no duality of interest associated with this manuscript.

References

1. The TRIGR Study Group (2007) Study design of the Trial to Reduce IDDM in the Genetically at Risk (TRIGR). Pediatr Diabetes 8:117–137
2. Åkerblom HK, Knip M, Becker D et al (2007) The TRIGR Trial: Testing the potential link between weaning diet and type 1 diabetes. Immunol Endocr Metab Agents Med Chem 7:251–263
3. Åkerblom HK, Virtanen SM, Ilonen J et al (2005) Dietary manipulation of beta cell autoimmunity in infants at increased risk of type 1 diabetes: a pilot study. Diabetologia 48:829–837
4. Norris JM, Barriga K, Klingensmith G et al (2003) Timing of initial cereal exposure in infancy and risk of islet autoimmunity. JAMA 290:1713–1720
5. Ziegler AG, Schmid S, Huber D, Hummel M, Bonifacio E (2003) Early infant feeding and risk of developing type 1 diabetes-associated autoantibodies. JAMA 290:1721–1728
6. Siljander HTA, Salonsaari R-T, Hekkala A et al (2010) Role of diabetic family history in the prediabetic autoimmune process in children recruited from the general population based on HLA-associated disease risk. Diabetologia 53(suppl 1): S180, abstract
7. Savilahti E, Akerblom HK, Tainio VM, Koskimies S (1988) Children with newly diagnosed insulin dependent diabetes mellitus have increased levels of cow's milk antibodies. Diab Res 7:137–140
8. Vaarala O, Saukkonen T, Savilahti E, Klemola T, Akerblom HK (1995) Development of immune response to cow's milk proteins in infants receiving cow's milk or hydrolyzed formula. J Allergy Clin Immunol 96:917–923
9. World Health Organization (1999) Definition, diagnosis, and classification of diabetes mellitus and its complications: report of a WHO consultation. World Health Organization, Geneva
10. Lorenzen T, Pociot F, Stilgren L et al (1998) Predictors of IDDM recurrence risk in offspring of Danish IDDM patients. Diabetologia 41:666–673
11. Harjutsalo V, Reunanen A, Tuomilehto J (2006) Differential transmission of type 1 diabetes from diabetic fathers and mothers to their offspring. Diabetes 55:1517–1524
12. The EURODIAB ACE Study Group and The EURODIAB ACE Substudy 2 Study Group (1998) Familial risk of type 1 diabetes in European children. Diabetologia 41:1151–1156