

## Editor's Corner

### Dear Study Families!

It is summer again, sun is shining and our Study is going on well. The oldest child is now 8 years old.

Principal Investigator Mikael Knip has put together a brief overview on prevention of type 1 diabetes in children and adolescents. There can be many alternative ways to prevent diabetes. North American Nutrition Coordinator Anita Nucci has analyzed breast feeding patterns in TRIGR families. Professor Jorma Ilonen briefs on the new genetic ancillary study. This study is planned to start at the beginning of next September, and it will require one additional blood sample at the next visit. I hope that you will have a favorable view on this request.

At the end brave young boy, Liam, shows us how the glucose tolerance test (OGTT) should be done properly.

Matti Koski  
Chief Editor

riences, the prediabetic period lasts on an average approximately 3 years among those subjects who develop clinical diabetes in childhood.

### *Different preventive strategies*

Preventive treatments can be classified into primary, secondary and tertiary prevention. Primary prevention covers treatments aimed at preventing the initiation of the diabetic disease process e.g. among those who carry genetic disease predisposition. Secondary prevention refers to modalities aimed at inhibiting the progression of the disease process to overt disease in subjects who already have predictive markers of diabetes, i.e. diabetes-associated autoantibodies. Tertiary prevention focuses on individuals affected by overt disease by attempting to restore their insulin production.



### *Primary prevention*

There is accumulating evidence that some enteroviruses could cause beta-cell damage leading subsequently to type 1 diabetes. Based on these observations attempts to develop an enterovirus vaccine that could prevent infections causing type 1 diabetes have been launched. If the initiation of the disease process could be eliminated, type 1 diabetes should never become manifest. The vaccination project is based on a unique observational Finnish birth cohort study (Diabetes Prediction and Prevention, DIPP), but it will still take years before we can expect to have an efficient and safe vaccination available for clinical use. If such a vaccine comes true, one has to decide whether all infants should be vaccinated or only those who are at genetic risk for type 1 diabetes.

There are many studies supporting the hypothesis that early nutrition has an impact on diabetes risk. Especially early exposure to foreign proteins seems to increase the risk. In TRIGR we are studying the question whether weaning to a highly hydrolyzed formula decreases the risk of developing diabetes-associated autoantibodies by the age of 6 years and type 1 diabetes by the age of 10 years. We will have an answer to the first question in 2013 and to the second conclusive question in 2017. We have now results from the TRIGR pilot study, according to which weaning to an extensively hydrolyzed formula reduces the cumulative incidence of predictive autoantibodies with 50 % by the age of 5 years.

Another pilot trial modifying early feeding has been performed in Finland. The FINDIA study set out to assess whether weaning to a cow's milk formula without bovine insulin can decrease the development of diabetes-associated autoantibodies. Bovine insulin that is present

## Prevention of type 1 diabetes in children and adolescents: past and future perspectives

### **Prediabetes**

Type 1 diabetes is an autoimmune disease characterized by gradual destruction of the insulin producing cells until the body's own insulin production is unable to keep blood glucose concentrations at a normal level. At that point the child develops symptoms of high blood glucose: he or she drinks a lot, passes water frequently, and is more tired than earlier. Before the symptoms appear, there is an asymptomatic period during which the insulin producing cells are destroyed without causing any symptoms. It has been estimated that when the child starts to have symptoms of diabetes, only about 15-20% of the insulin producing cells are still functional. The shortest prediabetic period that we have experienced in previous studies has been a couple of months; in that case a baby who seroconverted to positivity for diabetes-associated autoantibodies at the age of 10 months presented with symptoms of clinical diabetes at the age of 12 months. The longest prediabetic period that we have witnessed so far lasted for 21 years; a girl who was observed to be autoantibody positive for the first time at the age of 11 years presented with diabetes at the age of 32 years. Based on our experi-

in normal cow's milk based formulas differs from human insulin by three amino acids. The impetus for this study was the observation that young children who developed diabetes-associated autoantibodies appeared to lack the capacity to mount oral tolerance to bovine insulin when the exposure continued in infancy and early childhood. This raises the question whether the immune response initially provoked by bovine insulin may turn towards the endogenous insulin-producing cells. Is so, bovine insulin might act as a disease promoting dietary factor similar to the role of gluten in celiac disease. The results of the FINDIA pilot trial will become available this year.

An American pilot study (Nutritional Intervention for the Prevention of Type 1 Diabetes, NIP) is testing the hypothesis that dietary supplementation with an omega-3 fatty acid (docosahexaenoic acid) during fetal life and in infancy will slow down the inflammation associated with the diabetic disease process. About 100 children with an HLA-genotype predisposing to type 1 diabetes and with a family member affected by type 1 diabetes have been randomized to this study. Some studies have implicated that the lack of vitamin D in infancy increases the later risk of type 1 diabetes. A pilot study based on high daily supplementation with vitamin D (2000 IU) has been conducted in Canada to test the feasibility of such a strategy.

### **Secondary prevention**

Secondary prevention trials have tested whether it is possible to slow down the disease process by giving a small dose of subcutaneous or oral insulin. The outcome was negative, as these treatments had no significant effect on the progression rate to clinical diabetes. A subgroup analysis showed, however, that the administration of oral insulin decreased the progression to overt diseases among those individuals who had high titers of insulin autoantibodies (IAA) before the start of the intervention. Accordingly a new larger trial aimed at preventing progression to clinical diabetes by oral insulin has been started in relatives of patients with established type 1 diabetes provided that the relative tests strongly positive for IAA. In the DIPP study children testing positive for at least two diabetes-associated autoantibodies were treated with nasal insulin. The treatment turned out to be ineffective also among those with high IAA titers. The ENDIT trial treated autoantibody positive family members with a megadose of vitamin B (nicotinamide). No effect was observed on the progression rate to clinical diabetes over a 5-year follow-up period.

The experience so far from secondary prevention trials indicates that diabetes prevention is challenging and may require the combination of several different treatments. Full-scale primary and secondary prevention trials require large study populations and long follow-up periods. Therefore the scientific community has focused in recent years on tertiary trials which set out to test the effect of various treatment modalities on the preservation of the endogenous insulin secretion in patients with newly diagnosed type 1 diabetes. If a protective effect can be observed and confirmed, the next step would be to test the effect of such a therapy on progression to overt diabetes among subjects with preclinical disease.

### **Tertiary prevention**

It has been shown that there are several treatment options which seem to delay the decrease in the own insulin production commonly seen over the first years in patients with newly diagnosed type 1 diabetes. Anti-CD3 and anti-CD20 monoclonal antibodies as well as GAD-vaccination have been reported to reduce the rate of decline in endogenous insulin secretion in patients with newly diagnosed diabetes. The two first options are associated with a series of side effects and therefore it is not possible to perform blinded trials. In contrast, the GAD-vaccine seems to be safe, at least when treated patients have been monitored over the first few years after treatment. It is typical for this kind of treatments that they can potentially delay the disease progression, but none has so far been able to cure the disease. In addition, these trials have been conducted in adults and adolescents, and not in young children who appear to have the most aggressive and rapid disease progression.

### **Future perspectives**

Past experiences support the view that primary prevention might be more effective than secondary or tertiary prevention, since it must be easier to prevent the initiation of the disease process than to try to stop it. Although there are currently no treatments for clinical use, I am convinced that the future will provide effective treatments for primary, secondary and tertiary prevention of type 1 diabetes. That is a challenging goal, and most likely there will be many blocks and disappointments on the road, but type 1 diabetes will some day be a beatable disease.



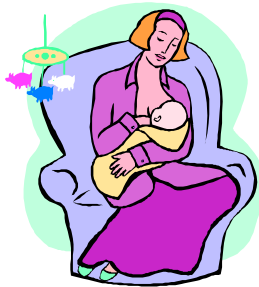
*Mikael Knip  
Principal Investigator*

## **The Patterns of Breastfeeding in TRIGR**

Breastfeeding is associated with many health benefits for infants and their mothers. Although breastfed infants have a lower risk of respiratory infections than non-breastfed infants, the relationship between breastfeeding and chronic conditions such as diabetes, asthma and allergies is controversial. Nevertheless, exclusive breastfeeding for at least 4 months and delaying the introduction of foods until 4-6 months of age is recommended for infants who are at high-risk for these conditions. The World Health Organization (WHO) and the American Academy of Pediatrics (AAP) both recommend exclusive breastfeeding for all infants for the first 6 months of life and then supplemented breastfeeding for at least one year and up to two years or more.



Previous studies have shown that women with type 1 diabetes are less likely to breastfeed their children or breastfeed for a shorter period of time than women who do not have diabetes. Almost all (90%) of the TRIGR infants were breastfed after they were born. This finding may be due to TRIGR families being more familiar with the evidence that breastfeeding may protect children from type 1 diabetes. The rate of breastfeeding in TRIGR infants was lower at 6 months of age among mothers with diabetes (50%) than those who did not have diabetes (72%). However, this finding was not the result of the mother having diabetes. In general, mothers who did not exclusively breastfeed during the first few days of life, who delivered early and who were of a younger age had a shorter duration of breastfeeding. In the TRIGR study, more mothers with diabetes had these characteristics. Caesarean delivery has also been associated with a shorter duration of breastfeeding. We observed this situation in the TRIGR study as well.



Maintenance of blood glucose control during breastfeeding in mothers with type 1 diabetes is important because high glucose concentrations may affect the secretion of prolactin, the hormone that stimulates milk production. In addition to good blood sugar control, successful breastfeeding can be accomplished with both an early start of breastfeeding as well as an increased frequency of breastfeeding. For the many short-term and potential long-term benefits to infants and their mothers, breastfeeding should be encouraged and supported in all pregnant women.

*Submitted by:  
The TRIGR Nutrition Intervention Committee*



*Anita Nucci  
Assistant Professor  
Nutrition Coordinator, North America*

## The Genetic ancillary study in TRIGR project

It is well known that type 1 diabetes is associated with a strong genetic component. It has been known for more than 30 years that the most important risk genes are located in the HLA region on the human chromosome 6. The children taking part in the TRIGR study have already been screened for the HLA-DQ gene alleles associated with type 1 diabetes risk.

Our understanding of the susceptibility associated genes has increased considerably during the last years. We have learned to know the existence of several new risk genes including the gene coding for insulin (INS) and genes affecting lymphocyte activation like IL2R, PTPN22 and CTLA4. Also the genes within the HLA region can now be more exactly defined. It is extremely interesting that certain gene alleles and their combinations seem to be associated with specific pathogenic mechanisms and the effects of environmental factors favouring disease development. Certain gene polymorphisms could thus be markers of increased vulnerability associated with viral infections and others of the risk associated with specific nutritional factors.

It is thus important for the TRIGR project to collect more information on the genetic disease susceptibility of participating children. The study is aimed to clarify the possible role of one specific environmental factor, intact cow's milk proteins contained in the control formula and hydrolyzed in the study formula. It is likely that this mechanistic pathway in the disease pathogenesis is associated with certain specific genetic factors. The definition of all type 1 diabetes associated genetic polymorphisms is thus helpful for the analysis and understanding of the results generated by the study. This is why we have now launched the genetic ancillary study and are asking all participating families to accept the collection of an additional blood sample from the participating child at the next Study Center visit.



*Jorma Ilonen  
Professor  
Special Investigator*



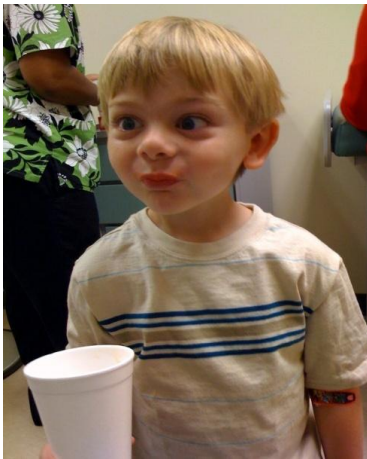
**LIAM doing his OGTT**



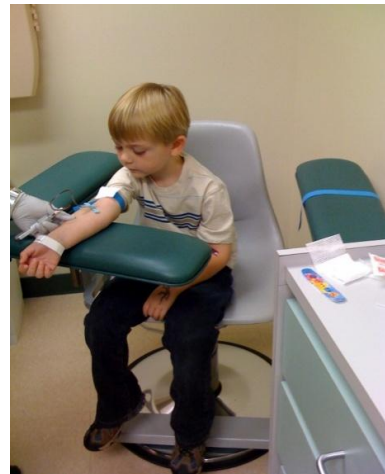
**I'M STILL A LITTLE SLEEPY!**



**THIS GLUCOSE DRINK IS NOT THAT BAD!**



**LITTLE BIT OF A SUGAR RUSH!**



**I'M WATCHING. THEY ONLY GET ONE SHOT AT THIS. NOW THAT I'M AWAKE**

**DONE!**

