

Editor's corner

Dear Study Families!

In this issue we are discussing why is type 1 diabetes increasing in children. Professor Outi Vaarala will present her view on this subject.

Traditional growth charts are very important tools especially for pediatricians to identify potential health problems in children and adolescents. Our Study dietitian Tammy Cooper from Canada has submitted a report on the World Health Organization (WHO) Growth Charts that have been adapted for use in Canada.

The TRIGR Study was originally planned to be completed when the child reaches the age of 10-years. It has been now decided to continue the follow up until all the children will be 10-year old (February 2017). When the study has been completed the families will be informed what kind of study formula the child has received. During the extended period there will be one annual visit with the same blood tests as earlier. An additional glucose tolerance test will be performed at the last study visit if it has not been done within the preceding year. The extended follow-up will make it possible to assess how puberty may affect the study outcome, i.e. the appearance of autoantibodies and the development of type 1 diabetes. We know from before that puberty affects insulin sensitivity by inducing resistance to insulin in its target organs (liver, muscles and fat tissue) and this may have an impact on progression to type 1 diabetes. In addition the extended follow-up will increase the statistical power of the trial, in other words, the final result will become more reliable. Therefore it is important that all the participating families will stay in the study all the way to year 2017. A warm thank to all of you in advance!

Matti Koski
Chief Editor

Why is type 1 diabetes increasing in children?

Type 1 diabetes is increasing world-wide. These kind of rapid changes in disease incidence are not explained by genetic factors but are most likely related to the alterations in the environmental factors

which contribute to the development of type 1 diabetes. Early introduction of cow's milk proteins and wheat proteins as well as enterovirus infections have been linked to the risk of type 1 diabetes and present the candidate environmental factors of interest.

The importance of cow's milk in the risk of type 1 diabetes

Our research group has explored the link between cow's milk and type 1 diabetes. In several studies, the early introduction of cow's milk proteins before the age of 2-3 months has been associated with the increased risk of type 1 diabetes. These epidemiological findings have not been reported in all studies performed and thus the link between cow's milk and type 1 diabetes is under eager investigation and debate in the scientific society.



In healthy individuals tolerance to food proteins develops with age when the mechanisms of immune regulation are activated. In food allergies and in celiac disease, tolerance to food antigens is immune-mediated, and it can be seen as increased intestinal inflammation when exposed to food allergens in allergies or wheat gliadin in celiac disease. The factors which interfere with the development and maintenance of intestinal tolerance are not fully understood.

We have studied whether avoidance of cow's milk insulin, i.e. bovine insulin, in the diet of infants at genetic risk of type 1 diabetes could reduce the appearance of type 1 diabetes related autoantibodies. In the FINDIA-pilot study we have used a special formula from which bovine insulin has been removed. Three amino acids are different in bovine insulin in comparison with human insulin and thus our immune system develops easily antibodies to bovine insulin. Our studies suggest that early exposure to bovine insulin in cow's milk products could explain the link between cow's milk and risk of type 1 diabetes. In the TRIGR pilot study the immune response to bovine insulin was lower in children who received hydrolyzed casein-based formula than in children who were given regular cow's milk formula, which indicates that bovine insulin is hydrolyzed as other proteins in the TRIGR test formula.

Breast milk contains also insulin, namely human insulin. Human insulin is less immunogenic and the antibody levels to human and bovine insulin are lower in breast-fed children when compared to formula-fed children. It is possible that human insulin in breast milk is beneficial and is capable to induce tolerance to insulin. Insulin may also contribute to the maturation of the gut.

When we compared the development of antibodies binding to bovine insulin between children who developed later in their life type 1 diabetes related autoimmunity and children who remained autoantibody negative, we found that the levels of antibodies binding to insulin increased during infancy whereas the levels remain stable or decreased in the children who remained autoantibody negative during the follow-up. These results suggest that tolerance to dietary insulin is altered already during early life in children who later develop beta-cell autoimmunity. Similarly, in the TRIGR pilot study we observed that the children who developed type 1 diabetes by age 7 years had higher levels of antibodies to cow's milk proteins already at the age of 9 to 12 months when compared to the children who remained non-diabetic. These studies show that impaired tolerance to food antigens is associated with type 1 diabetes and seems to be an early marker of disease susceptibility.

Gut plays a key role in type 1 diabetes

The gut immune system has been demonstrated to play a key role in the regulation of autoimmune diabetes in animal models. The development of autoimmune diabetes can be prevented by dietary treatments. When hydrolyzed proteins are introduced at weaning in diabetes prone mice or rats instead of whole proteins the development of diabetes is markedly reduced.

The way how the gut immune system handles dietary proteins and insulin during the first 3 months of life seems to play a crucial role in terms of future risk of diabetes. The intestinal bacterial colonization and the gut closure take place gradually after birth. The mucosal surface is composed of epithelial cells and the junctions between these cells develop after birth which means that the gut is leaking food proteins extensively immediately after birth. Also the production of antibodies in the gut immune system develops gradually. Thus the response of the gut to foreign food proteins, such as cow's milk proteins, varies according to the age at exposure.

Our studies in Finnish children together with Italian studies demonstrate that children with established type 1 diabetes show intestinal immune alterations. In addition, children with type 1 diabetes and also children at risk of type 1 diabetes have increased gut permeability. It is important to find the factors which contribute to the development of intestinal

inflammation and increased permeability so that we could cure the intestinal inflammation. Accumulating evidence is showing that intestinal inflammation is a key regulator of type 1 diabetes development. The final evidence is, however, still missing. Prevention of autoimmune diabetes through the cure of intestinal inflammation would be the final proof.



Intestinal bacterial flora is important for the development of oral tolerance. It has been shown that oral tolerance develops poorly when the animals are in a microbe-free environment. The intestinal microbiota has changed conspicuously during the last decades in Western countries. The diet has also changed a lot, and the use of bacteria in the preservation of food has decreased. It seems that intestinal microbiota differs between children from different countries. In Estonian children the amount of fecal lactobacilli was higher than in Finnish children in the 90's. It is possible that the composition of intestinal microbiota plays a role in the development of tolerance to food proteins in humans. Interestingly in the animal models of autoimmune diabetes the role of intestinal microbiota seems to be important in the development of diabetes. The transfer of intestinal microbes that prevented the development of diabetes in an animal model transferred the protection to recipients of the microbes.

Why is type 1 diabetes increasing?

I answer this question based on the gut hypothesis that I have presented as stairs to type 1 diabetes. I would like to emphasize that the answer is based on hypotheses. The factors associated with the risk of type 1 diabetes, such as early exposure to cow's milk and wheat gliadin or enterovirus infections have not increased and thus these factors have not contributed to the risk of type 1 diabetes in a similar manner earlier when the disease was rare. Also currently many children are exposed to these factors and do not develop type 1 diabetes since these children have healthy tolerance to food proteins. However, a minority of children who have altered intestinal immunity and impaired tolerance to food proteins may develop intestinal inflammation and aberrant response to these proteins, which contribute to the risk of type 1 diabetes. The number of children who show impaired tolerance and intestinal inflammation increases in Finland and Western world likely due to changes in the factors that should support the establishment of oral tolerance. The true problems are related to the changes in the environmental microbial load, industrialized food production and changes in the food processing and preservation. Also environmental

toxins and chemicals may affect the mucosal surface and immune system. It would be important to characterize the changes in the gut immune system in type 1 diabetes and to find ways to prevent the development of these changes. In the TRIGR study we explore whether hydrolysed formula could contribute to the development of oral tolerance and thus reduce the risk of type 1 diabetes.



Outi Vaarala, professor of pediatric immunology

Mila Hyytinen has edited this chapter based on the lecture "Why type 1 diabetes is increasing?" which Outi Vaarala presented at the Meeting of Finnish Society of Sciences and Letters in November 2008.

World Health Organization (WHO) Growth Charts Adapted for Use in Canada

Regular growth monitoring is a routine part of medical care for all infants, children and teens and helps keep them in good health. Growth charts are used by pediatricians and other health care providers to follow a child's growth over time. Growth charts allow the height, weight, and head circumference of a child to be compared to that expected for children of the same age and gender to determine whether the child is growing appropriately. Growth charts can also be used to estimate a child's adult height because, in general, children maintain a fairly constant growth curve.

Until recently, Canada used growth charts which were created by the Center for Disease Control (CDC) using growth data collected in 1997. These growth charts were based on studies of formula-fed babies and were not specific to different race or ethnic groups.

In 2006, the World Health Organization (WHO) released new international growth charts for infants and children from birth to 5 years of age. These growth charts are based on studies of children living in six different countries (Brazil, Ghana, India, Norway, Oman and the USA). All the children in these studies had been raised according to recommended nutritional and health practices, including exclusive breast-feeding for the first 4-6 months of life. These studies determined that overall, breast-fed children grow at similar rates to bottle-fed infants, and that their growth pattern is the ideal one. Therefore, it was recommended that these

international growth standards be used for all children, regardless of whether the children are breast-fed or non-breast-fed.

There are some important differences in the WHO charts. First, they cover a wider age range for younger children. The transition to an older age growth chart now occurs at 5 years of age, compared to 2 years or 36 months for the CDC charts. Secondly, the WHO growth charts show that breast-fed infants gain weight more quickly in the first 6 months than non breast-fed infants, but breast-fed infants gain weight more slowly from 6 months to 1 year of age. This growth pattern is now accepted as normal which means that when non-breast-fed infants' growth is plotted on these charts, it may look like they are gaining weight too slowly or too quickly.

Height, weight, and head circumference have always been part of traditional growth charts. The new WHO growth charts also include BMI-for-age curves. The shape of BMI-for-age curves is somewhat different than for other growth indices in that BMI-for-age begins to decline after about 1 year of age and continues falling until it reaches a minimum around 4-6 years of age. BMI-for-age then begins a *gradual increase*, continuing through childhood and adolescence. Many research studies have linked high pediatric BMI to obesity and adverse health/outcomes in the future. While BMI is an effective screening tool for identifying children who may be at risk for overweight and obesity, it is important to know that BMI is not recommended as a diagnostic tool on its own.

Canadian health practitioners are now using the updated WHO growth charts adapted for Canada because they are more accurate for the Canadian population than the previous CDC growth charts. This reflects the trend of breast feeding in Canada. The new growth charts have been endorsed by the Collaborative Working Group (Canadian Pediatric Society, College of Family Physicians of Canada, Community Health Nurses of Canada, and the Dietitians of Canada).

For further information, check out these websites:
*Dietitians of Canada - www.dietitians.ca/growthcharts
Fact sheet for parents on interpreting children's growth -
Is my Child Growing Well? Questions and Answers for Parents*



*Submitted by Tammy Cooper, RD, CDE
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References:

<http://www.who.int/childgrowth/en/en>

http://www.who.int/childgrowth/standards/technical_report/en/index/htm

<http://www.statcan.gc.ca/concepts/health-sante/index/eng.htm>

<http://www.dietitians.ca/growthcharts>

Interview with Pepijn

We would like to report the story of Pepijn, who accompanied his brother Casper to the Sophia Children's Hospital Rotterdam. Casper is taking part in the TRIGR study and visited the hospital for the OGTT (6-year study visit). Badies Manai, who is the study nurse in the Dutch TRIGR team, conducted a short interview. The interview was done with the permission of Pepijn's parents. The interview was translated in English for the purpose of publication in the 'TRIGR Family News'. During the translation we tried to respect the language of Pepijn and his parents.

Pepijn is 10 years of age. He was diagnosed with type 1 diabetes when he was 2-year-old. Generally we see many siblings of TRIGR participants who accompany their brother/sister to our hospital for the OGTT. However we were impressed by Pepijn, because he is diabetic, and decided to postpone his breakfast and stayed with his brother during the OGTT.



Picture: Casper (left) and his brother Pepijn (right)

After obtaining his parents' consent a few days later we interviewed Pepijn to learn more about his motives.

Badies: How long have you had diabetes?

Pepijn: I was almost 2 years.

Mother: OK..., so you have it for 8 years.

Badies: What do you do when you have diabetes?

Pepijn: I have a needle (**insulin pump**), twice a week I need a new needle. I have to check myself a lot (**to check the blood sugar level**). It's not always nice. And before every meal I have to take extra insulin.

Badies: How do you take extra insulin?

Pepijn: With my insulin pump, the insulin then comes into my belly. That is why I have a needle.

Badies: Why do you have to check yourself?

Pepijn: To know if I have a low or high blood sugar.

Badies: What is high and what is low?

Pepijn: above 10 and below 4 (**mmol/l**).

Badies: How is it to live with diabetes?

Pepijn: I don't like it, but occasionally I do like it.

Badies: What is it you like?

Pepijn: When I am low (**hypoglycemic**), I can eat something extra. Especially sweets. But many times it is not fun.

Badies: What are the things you don't like about diabetes?

Pepijn: When I am too high or too low (**hyper- or hypoglycemic**). I think it is weird that Casper always sometimes says: "I want to have diabetes too". But when you have it, you don't want it anymore. Sometimes it's nice and sometimes it is not nice to have diabetes.

Badies: Why did you come along with your brother to the hospital?

Pepijn: I know how it is to be in hospital. And I thought if Casper has to go to the hospital, then he will have daddy, mummy and me with him!

Badies: And how was your visit to our hospital?

Pepijn: I liked watching the DVD very much, and with Casper it was fun too (**Pepijn and Casper both watched a DVD during the 2-hour waiting period**). I liked very much that this time the hospital visit wasn't for me.

Badies: Casper wasn't allowed to eat before the sugar test (**OGTT**). Why did you not eat?

Pepijn: Casper is very dear and I had decided beforehand, if Casper isn't allowed to eat, I won't eat either. Yes, that's what I thought, that he wouldn't be the only one who didn't have breakfast.

Badies: Did you find it hard or not so hard, or did you find it easy?

Pepijn: Well, first I thought it wouldn't be nice, but then it was nice, and then I got hungry, very very hungry.

Badies: And did you find that hard or easy?

Pepijn: At first it was easy, but after a while a little harder.

Badies: Would you join your brother next time when he has to come to the hospital for a sugar test?

Pepijn: Yes, I think so.

Badies: (**question to parents**) Would you like to add something?

Father: Because Pepijn has diabetes he felt the need to do something for Casper.

Mother: And with breakfast. Pepijn wouldn't eat breakfast in front of Casper. They both like their breakfast very much and yes, he wanted to share the experience with his brother.



Study Nurse Badies Manai
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