

TRIGR Family News

Editor's corner

Dear Study families,

Here we are with a new volume of the TRIGR Newsletter. Dr. Margaret Lawson, the Co-Principal Investigator in Canada has crystallized her thoughts about the benefits of being a participant in a research study. It is amazing that the influence of the studies is spread so widely in different fields, and you will also have significant advantage as a participating family in TRIGR.

We introduce the results from the FINDIA pilot trial. Professor Outi Vaarala is the Principal Investigator of that study, and she is also Special Investigator of TRIGR.

In the Kid's corner we have four stories about our participants from Germany.

Matti Koski
Chief Editor

The Benefits for Families from Participation in Research Studies

Why do children get type 1 diabetes? Every parent whose child has been diagnosed with type 1 diabetes asks this question. They usually follow this question with "Why my child?" and often they add, "Is it because of something I fed (or didn't feed) my child?" We know families are frustrated that we can't answer these questions. But when the TRIGR study is completed in 2017, we will have an answer to the question about infant nutrition, and every single TRIGR family will have made a major contribution to finding this answer. Thanks to the TRIGR families, we will finally know whether modifying early infant nutrition can lower a child's risk of developing type 1 diabetes.

Between 2002 and 2006, 5606 families made the decision to enroll in TRIGR through one of the 77 sites spread over 15 countries. After their child's birth and availability of the child's genetic (HLA) results, 2159 of these families agreed to continue in the TRIGR intervention and follow-up study, originally planned for 10 years and now extended until 2017. All together, these 2159 children have had about 25,000 study visits, about 22,000 blood tests, and about 1,500 Oral Glucose Tolerance Tests, making TRIGR one of the largest pediatric studies ever!

There is no doubt that the scientific community benefits when families participate in research. We learn more about the disease that is our life's work, and how to provide better care to our patients. We share our research findings with other health professionals by presenting and publishing the results. But what about the families and children who take part in research studies? How do they benefit from participating in research? Several researchers have examined this by interviewing families to learn about their experience taking part in research.

Advancing Science and Knowledge about Type 1 Diabetes

Families who participate in diabetes research studies say they like the fact that they are actively doing something to help researchers and doctors learn more about the condition that affects their family every day. TRIGR families know that because of their involvement in TRIGR, we will learn more about what causes type 1 diabetes and how to prevent it in other families. Even though this won't be the cure they want for themselves, their spouse or other child who already has type 1 diabetes, the knowledge we gain from TRIGR will help their children's children. Because of their participation in TRIGR, in the future we will be able to tell people who have type 1 diabetes in their family whether the use or avoidance of a specific type of infant formula can help to prevent diabetes.

Helping Future Generations of People with Type 1 Diabetes

Families who participate in research studies benefit from the knowledge that they are helping others. They know that research is dependent upon the goodwill of volunteers. Today's advances in diabetes management, which are already leading to fewer diabetes complications and longer and more normal lives for people with type 1 diabetes, happened

because people volunteered to be in studies such as the Diabetes Control and Complications Trial (DCCT). The only way we will find better treatments for people living with type 1 diabetes, and the cure for type 1 diabetes that everyone wants, is if people volunteer to participate in research studies. TRIGR families are helping future generations of parents, just like previous generations of people with type 1 diabetes helped discover the benefits and safety of today's insulins, blood glucose testing methods, and other diabetes technology.

Access to Information about their Child

TRIGR families also benefit from access to information they wouldn't otherwise have – such as the results of their yearly antibody tests, beginning after their child's 6th birthday and every year thereafter until the end of the TRIGR study. In addition, the local TRIGR staff provides support and counseling to families to help them understand the antibody results, as well as the hemoglobin A1c and blood glucose test results. Families tell us how important this information is to them, regardless of whether the results are positive or negative, as “information is power” and provides them with a sense of control while they wait to see whether their child will or will not develop diabetes. Families who had difficulty with the TRIGR blood tests when their children were younger have re-joined TRIGR because they want to receive this information, and continue to have annual antibody testing through the TRIGR study.

Potential Benefit for Their Child

These antibody results and other blood tests help the TRIGR staff to counsel families about their child's risk for developing diabetes over the next year. If the test results suggest that the child's risk of developing diabetes may have increased, parents can watch more closely for signs of diabetes such as increased urination, increased thirst, and weight loss, and they can seek medical attention before the child becomes seriously ill and develops diabetic ketoacidosis (DKA). Other research studies have shown that children who participate in diabetes studies like TRIGR are less likely to develop DKA at diabetes onset because diabetes is diagnosed at an earlier stage before the child becomes sick.

The Opportunity for Children to Learn How Research is Done

Children learn about science in school, and through involvement in activities like school science projects. Participating in TRIGR enables them to learn about science through personal experience, seeing first-hand what research involves, and the commitment that it requires from children and parents. Other research studies have shown us that siblings of children with type 1 diabetes often wish they could help their sibling. Being part of TRIGR allows TRIGR children to contribute to science and to help TRIGR staff to learn more about the condition that their parent or sibling has.

A Chance to be Part of Medical History

TRIGR children and their families are making medical history! We are so grateful to each and every one of you for the part you are playing in making TRIGR a success. Each family's contribution is so important and critical to us answering the TRIGR questions about the link between infant feeding and the development of type 1 diabetes. In the future, other families will benefit from what you have done, and they too will see that participation in research benefits all of us!



Margaret Lawson, MD, MSc, FRCP, Co-Principal Investigator, TRIGR Canada

Sources

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Bovine insulin and type 1 diabetes

The Finnish Dietary Intervention Pilot Trial for the Prevention of Type 1 Diabetes (FINDIA) studied whether weaning to a bovine insulin-free cow's milk formula reduces type 1 diabetes associated autoantibodies in children at genetic risk. Newborn infants were enrolled into the FINDIA study in 2002-2005 and observed up to the age of 3 years.

A total of 1113 infants carrying a HLA-risk genotype to type 1 diabetes were randomly assigned to receive study infant formulas after 9 infants were withdrawn: cow's milk formula (CMF) (n = 389), whey-based hydrolyzed formula (WHF)

(n = 350), or whey-based FINDIA formula essentially free of bovine insulin (n = 365) during the first 6 months of life whenever breast milk was not available. All infant foods containing cow's milk or beef were excluded from the child's diet during the intervention period. Autoantibodies to insulin (IAA), the glutamic acid decarboxylase (GADA), and the tyrosine phosphatase-related IA-2 molecule (IA-2A) were screened. If the primary screening test result was positive for at least one autoantibody, the islet cell autoantibodies (ICA) and autoantibodies to zinc transporter 8 (ZnT8A) were analyzed.

Weaning to an insulin-free CMF reduced the incidence of autoantibodies by age 3 years in children at genetic risk of type 1 diabetes mellitus in comparison with ordinary CMF. All together 6.3% of the children in the CMF group, 4.9% of those in the WHF group, and 2.6% of the children in the FINDIA group tested positive for at least one autoantibody by the age of 3 years.

Earlier studies have also shown that exposure to bovine insulin in cow's milk formula induced immunological reactions to insulin in formula-fed infants. Bovine insulin differs from human insulin in three amino acids. In humans, the immunogenicity of bovine insulin was recognized decades ago when used as therapy in patients with type 1 diabetes.

According to the hypothesis presented by Prof. Outi Vaarala, immunological reaction to dietary bovine insulin may develop in infancy when the gut is immature and permeable so that foreign proteins pass the mucosal barrier. Tolerance to dietary antigens develops by age, and it is also supported by breastfeeding. During the first months, gut permeability decreases and the number of IgA plasma cells increases leading to improved tolerance to food antigens.

In the TRIGR pilot study the use of hydrolyzed formula was associated with a decreased risk of diabetes associated autoantibodies. In the FINDIA study only insulin-free formula decreased autoantibodies significantly, but whey-based hydrolyzed formula did not. In TRIGR a casein hydrolysate is used, and it may differ from whey-based hydrolysate used in the FINDIA study. Casein-based hydrolyzed formula has been shown to decrease gut permeability and modify intestinal microbiota in animal models.

Study Monitor Mila Hyytinen

Reference: Vaarala O, et al. Removal of Bovine Insulin From Cow's Milk Formula and Early Initiation of Beta-Cell Autoimmunity in the FINDIA Pilot Study. Arch Pediatr Adolesc Med 166:608-614, 2012

Kid's corner

Hello, my name is Julian. I will be 10 year-old soon. I live on a big farm with lots of dairy cows and calves. When we harvest silage, I am sometimes allowed to ride on the passenger seat of the tractor. I like to drive with my Dinocar or play Floorball. I love to play with my little brother Jesse. We have lots of big and small toy tractors. On holiday we often go to the Baltic Sea, because I love water. In the evenings we play board games together with my parents and my granny from Berlin. In the beginning I didn't like being in the TRIGR study, because I was always afraid of having my blood test. But just before the appointment I always get a magic Band-Aid that I stick on just before my blood test. This numbs my skin so I don't feel any pain. It's great and now I'm not scared anymore.

Yours Julian



Hi, I'm Anouk. I live on a farm in a small village near Wolfsburg in Lower Saxony. I am 9 year-old and in fourth grade. I have a small pony named "Flecky". Santa Claus brought it me 3 years ago. I take riding lessons with my friend every Friday. My hobbies are riding, vaulting (sport with horse) and drawing. I go to art school (the "Mice-Workshop" in Sül-feld), where I have done etchings. Etchings are complex prints. First we scratch our designs into a metal plate, then paint them with different colours before printing them. Our class has already made beautiful calendars with our pictures and have won prizes. Here is a picture of one of my etchings. When I grow up I would like to become an artist. During my free time, I play with my brothers, sisters and friends. We have lots of hiding places in our yard where we sometimes secretly eat candies or just laze around. Of course I have to look after my pony too. Every day it has to be taken out of the paddock to be cleaned then we have to clean the horse stable. I walk to school every day with my friends Jacob and Pauline. Our small village school is fun. We have only 16 students in our class. This year we have

started to learn Spanish. We also had a great class trip to the Altenhausen castle. So, that's about me - and what do you do?

Yours, Anouk



Hello, my name is Joelle. I'm 10 year-old. I live in Bad Pyrmont-Kleinenberg, and I am in the 5th grade at the Humboldt High School. My brother Niklas has had type 1 diabetes since he was 18 month-old. I'm the first TRIGR child at the TRIGR center in Hannover (Kinderkrankenhaus auf der Bult). The first TRIGR-visit was done in my home. Since then I have gone to the outpatient care clinic in Hannover with my brother. Usually I get a small present after the visit or we go to the Zoo. During my leisure time I love riding or singing in a choir. I am also active at the youth fire brigade. This summer I was given the main child role of "Johanna" in the musical "Pope Joan" after succesful casting. So far, more than 20,000 spectators have watched the performances in Hameln with Sabrina Weckerlin in the leading role. She is a role model for me. We play on a revolving stage with many different sets. It's always very exciting when the curtain goes up, and my stage fright is usually gone after the first sentence has been pronounced. It is a truly amazing experience from makeup to the sound-check and then until the final applause. I am so happy to be able to have this experience in the musical world.

Yours Joelle, first German TRIGR child



*This is me with Dr Kordonouri
and Ms Semler*



Have you found me?



That is me with Sabrina Weckerlin

Hello, my name is Luca. I am 10 years-old. I have been taking part in the TRIGR study since I was born. Both my father and mother have type 1 diabetes and so far I am fortunate not having diabetes.

During my leisure time I play drums and take drum lessons once a week. I have played for 4 years in a handball team named MTV Ahrensböök. I started in the ballgame team, then I played in the Mini-Mix team for 2 years and now I am playing my second year in the male E-Youth group. The new season will begin this coming weekend. This year I started riding on a wakeboard at a water-ski facility. In the near future I want to try to jump off a ramp with my wakeboard. I feel school is currently very hard because I am just starting 4th grade. Sometimes on the weekends I go fishing with my dad to the "Großen Plöner See" (Great Plöner Lake), where we have caught many perches and pikes. I also ride with my dad on his motorbike through the "Holsteinsche Schweiz". I have a small, white Maltese dog named Emma. Sometimes I play catch with her. I like to play outside with my friends too. This year I visited the Hannover TRIGR center for the first time and met many friendly people. I met Ms. Aschemeier from the TRIGR team, who has been in contact with me and my parents for many years.

Yours, Luca

