Trial to Reduce IDDM in the Genetically at Risk

Autumn 2006
www.trigr.org

TRIGR Family News

Dear Reader

Up to the time being the TRIGR-study has had regional publications (Canada, Europe & Australia and USA) and some of the newsletters have been translated into local languages (remember we have 15 countries in our study). Since we are all part of the same unique trial with common interests and goals, we have decided to join our forces and create one common newsletter named TRIGR Family News.

The purpose of this leaflet is to update you on what is happening in our study, and what issues are coming up related to our study worldwide, to provide stories from families in various countries, questions and answers and naturally practical nutritional advices. If you have any ideas to improve our TRIGR Family News, please contact us!

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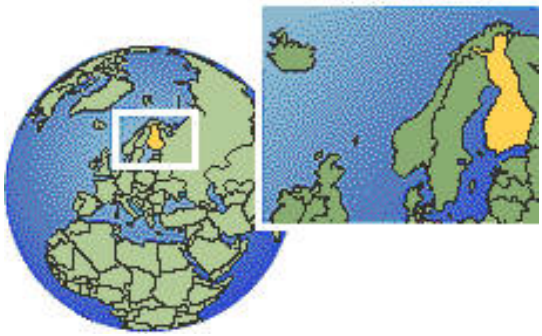
Nutrition and diabetes in children

Professor Suvi M. Virtanen, MD, PhD
Nutrition Special Investigator in
TRIGR, Finland

The continuously increasing incidence of type 1 diabetes (annual number of new cases of type 1 diabetes/100.000 children) seen in many industrialized countries over the last decades cannot be explained solely by genetic factors. Among environmental factors nutritional exposures and virus infections are the most strongly suspected ones. Short breastfeeding, early supplementary feeding, increased weight and height gain during childhood, and low vitamin D intake are factors that have been implicated to contribute to an increased risk of diabetes. However, the results of various studies vary largely, and no definite conclusions can be drawn at the present time.



One may wonder why we have not yet identified any firm risk factors for type 1 diabetes despite several decades of intensive research. Although type 1 diabetes is increasing rapidly in many populations, it is still a rare disease, and therefore large numbers of study subjects and long follow-up timess are needed in studies searching for the risk determinants of the disease. Compared to other study types randomized clinical trials provide the strongest evidence for a causal relationship. Randomization ensures that the groups to be compared are on an average similar regarding all other factors than the studied intervention (in case of TRIGR the infant formula). So far very few randomized trials have been performed in the field of prevention of type 1 diabetes. Actually TRIGR is the first nutritional primary prevention trial in the world, i.e. the first study in which there is an effort to pre-

vent type 1 diabetes in subjects who do not have any signs of diabetes when entering the study.

Now that most of the families taking part in TRIGR have gone through the intervention phase it is time to congratulate you for your achievement, and wish good luck and patience for the families who are still working with the intervention. Your efforts are still needed to complete the follow-up and to make it possible for us to find together an answer whether there will be a possibility to prevent type 1 diabetes. All the information you have been/are giving to us in interview calls and visits will be very crucial for us when analyzing the final results of the study. We have been delighted to find out that the breastfeeding rates are conspicuously high in TRIGR. The experience from other studies indicates that breastfeeding is more difficult for mothers with diabetes than for non-diabetic mothers, and the breastfeeding rates are usually lower among the affected mothers. However, in TRIGR an equally high proportion of diabetic and non-diabetic mothers (95%) start to breastfeed. At 6 months still 50% of the diabetic and 71% of the non-diabetic mothers continue to breastfeed. Even though a somewhat smaller proportion of the diabetic than the non-diabetic mothers continue to breastfeed, our figures for diabetic mothers are similar or higher than figures from other studies for the general population.

My sincere thanks to all of you, and looking forward to a continuous good collaboration!

Dear Peggy and all else with the TRIGR study

TRIGR Study
Peggy Franciscus, RN
Children's Hospital
University of Pittsburgh
Pittsburgh, USA

I want to start out by thanking you all for everything you have done to help my son, Logan Alexander, and myself. Without your help throughout this study so far, I know we would not be where we are in our lives right now. Being a young, single mother, full-time college student, and part-time Assistant Director of a dementia and Alzheimer's unit, you can imagine things have not been easy. But thanks to all of you, we are making it through our day's one at a time. Without the help of the formula provided for the first year of Logan's life, all the supporting words and cards, and friendly words of guidance, I know that I may not have made it as far as I have being a mother.

However, the most rewarding part of knowing I am being helped, is knowing, that we have been able to help in making a difference in other's lives in return.

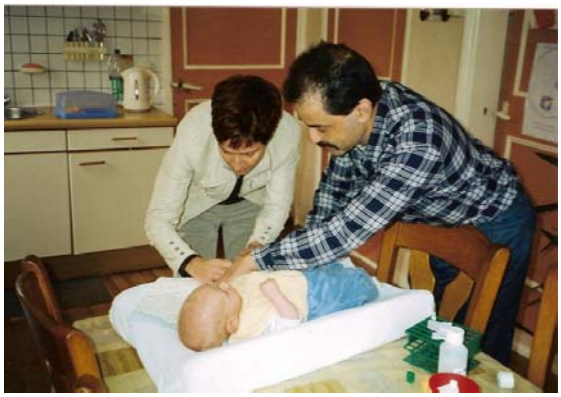
Getting monthly phone calls by the nurses and dietitians, not only let us know that others want to make sure things are going well for us, but also that we are cared about. It is a tremendous feeling. Logan is now around the corner from turning 15 months, and growing like you would not believe. He is close to 32 lbs and 33" (2'9") tall. He is running around, learning to speak, and making a huge smile grow wider on my face as every day passes.
I just want to thank all of those who are behind the scenes and on the scenes of making this study run. I admire each and every one of you and thank you from the bottom of my heart for all the differences you are making in others lives as well as my own. I know my son and I have been deeply blessed in becoming a part of this study, and I hope you all know how much of a difference you have made.

Thank you for everything!
Elizabeth

Preferring home visits over hospital visits

TRIGR Dutch Study group:Marit Verhagen, Dietician, Margriet Bisschoff and Badies Manaï, Research Nurses, and Jan Bruining, Professor, the Netherlands

Because of the longitudinal nature of the study, the Dutch TRIGR study team decided to perform study visits at home of the (potential) participants. By visiting the family before inclusion personal contacts are made and participation is clearly promoted.



This has implications for the long-term follow-up, namely to minimize the number of drop outs or lost to follow-up.

The addresses of most participating families in the Netherlands are located within a radius of approximately 95 miles of the study site in Rotterdam. Changes of addresses are easily to trace. We divided the country in a North and a South region. Margriet Bisschoff (RN) is appointed to the North and Badies Manaï (RN) to the South region, because of the location of their home addresses. When a study visit is scheduled Marit Verhagen (Dietician) accompanies Margriet or Badies. If this is not possible Margriet and Badies will visit the families together. We travel mostly by car outside rush hours.

The equipment we carry consists of source document forms for each subject, a tool kit with disposable blood sampling materials, and materials to store the blood samples until their shipment. All equipment is regularly checked. Upon request we provide the families with study formula.

Parents are always very welcoming. Because of their interest in the study, time is taken to answer their questions about the study progress. Parents are also willing to discuss the growth and development of their child. The medical history of the child is reviewed and the child is observed for signs of illness. Sometimes parents ask us questions about health care issues of their child. Mostly we provide basic advice. In some cases we ask parents to consult their family doctor. Marit performs the dietary interview according to the protocol. Parents are given the opportunity to talk about nutritional problems, even if these problems are not related to the use of the study formula.

Blood sampling is usually performed in the living room or the bedroom of the family. Sufficient time is taken to make all necessary preparations. In this phase it is important to give information to the parents about the procedure and possible perceptions of the child. We always invite the mother to stay near the child to provide comfort. When old enough, the child can sit on the parent's lap. If the first attempt is not successful a capillary blood sample is taken. Some parents encourage us, however, to make a second attempt to draw blood venously. Afterwards parents are given time to talk about the procedure. This way we learn about each parent's feelings and concerns regarding this procedure. At the end of the visit study forms are completed and a new follow-up appointment is agreed upon. When a child has his or her birthday we make sure we have a little present to give to the child. At our office we keep a birthday calendar and every child receives a birthday card annually.
Meeting parents and child at home for study visits clearly has advantages for the long term follow-up of study participants. This will have implications for the final outcome of the TRIGR study. We on the other hand can learn to know the families, interests, motives and concerns.

TRIGR in Canada

Written by Gigi Lough, Project Manager, TRIGR Canada

As many Canadian TRIGR families know, the Canadian Central Administration and Coordination of TRIGR takes place in two cities, London and Ottawa, Ontario. TRIGR Canada is lead by our Chair and Lead Principal Investigator, Dr. John Dupré and is assisted by Debra Nielsen. Dr. Dupré and Debra Nielsen are located at the Robarts Institute in London, Ontario. They work very hard for all the Canadian Centres at an International and National level. In Ottawa, located at the Children's Hospital of Eastern Ontario, TRIGR Canada's operation is coordinated by Dr. Margaret Lawson and Gigi Lough RN. Dr. Lawson is a Paediatric Endocrinologist with 14 years of experience in both clinical diabetes and diabetes research. Dr. Lawson started with TRIGR 7 years ago and sits on two TRIGR committees. Gigi Lough works as Project Manager for TRIGR Canada and as the Ottawa Study Coordinator. Her role includes the maintenance of direct communication with all the clinical centres in Canada, and with the U.S. and European Trial Coordinators. She takes part in clinic monitoring and site visiting and communications with the Data Management Unit in Tampa, Florida.

Canada has 18 TRIGR centres across the country starting from St. John's, Newfoundland in the East to Victoria on Vancouver Island, British Columbia in the West, with centres in all provinces from coast to coast. Canada has TRIGR families that travel from as far away as Whitehorse, Yukon to Edmonton by air or some families can travel as much as 12 hours by car. TRIGR appreciates all efforts families make to provide information and important blood samples for TRIGR.

TRIGR Canada recognizes 4 milestones. The first two milestones for TRIGR Canada were in June 2002. TRIGR Canada enrolled their first TRIGR baby in Ottawa and TRIGR Canada had the first HLA eligible baby, in North America, also located in Ottawa. The next milestone is that TRIGR Canada leads as the country with the highest number of HLA eligible babies with more than 500 Canadian babies in TRIGR. Our TRIGR centre located in Toronto, Ontario leads internationally as the centre with the most HLA eligible babies having well over 100 HLA eligible babies – what an accomplishment!

During the past 4 ½ years of recruitment and follow-up visits, TRIGR Canada has welcomed over 500 HLA eligible babies. We have welcomed other TRIGR families who moved from Australia and United States. As well, TRIGR Canada has said farewell to some Canadian TRIGR families who have moved to continue the study in the United States.

TRIGR Canada would like to take this opportunity to say THANK-YOU to our families for the continuing support they give to this important international trial, the first ever prevention study of Type 1 diabetes.

TRIGR in Australia

My Husband and I saw a story of the TRIGR study on the news when I was in the last trimester with our third child Brielle. With Brielle's Father and Grandfather both having type1 diabetes, we were more than happy to be involved in the study, in hope that we can contribute to help find a cure.

Living only 45 minutes away from Westmead Children's Hospital, I get to see the whole team Dr Neville Howard, Glenda Fraser & Ros Bongiorno, which is a delight.

Brielle was mainly breastfed, apart from the odd top up bottle of the study formula she had. Ros & Glenda, keep regular contact with Brielle's progress in between TRIGR visits, they are so very helpful with anything we need help with.

The blood tests can be hard, but I know it is all for a good cause, knowing that Brielle is being closely monitored for any underlining signs of diabetes is very reassuring.

Josh and I are very proud to be involved with TRIGR study, and I am sure Brielle will be in years to come (despite the blood tests). And hopefully by being involved, we have helped in finding the much needed cure for diabetes for our future generation.

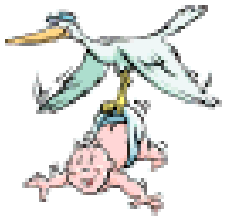
The Sinclair Family
Josh, Jennie, Jordan, Kieran & Brielle

Currans Hill
N.S.W. Australia

Where are we now?

Our target in the TRIGR trial was to gain altogether 2032 randomized children with increased risk for type 1 diabetes. On September 4, 2006 we reached the target. **Congratulations!** We have done more than we planned in the beginning. On September 30, 2006 2064 continued in the study after the genetic analysis. Somewhat more subjects were ineligible (58%).

We will continue to recruit families to the study provided that the expected date of birth is before the end of year 2006 (December 31, 2006 being the last possible date) to make the study statistically even more powerful.



Families in the study

The family history of the children who are continuing in the study at the end of September 2006 is presented in the table opposite. We have quite a lot more families participating where the mother is affected by type 1 diabetes than families where the father is affected. This varies greatly between countries.

If we compare two regions (North America and Europe+Australia), we can see that in the proportion of "Mother only" affected is 52% in North America and 47% in Europe+Australia. The corresponding share of "Sibling only" is 16% (NA) and 12% (EA), respectively.

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In contrast for example in Finland the proportion of "Father only" affected (53%) is clearly higher than that of "Mother only" affected (36%), while the share of "Sibling only" is quite modest (9%).

TRIGR
Accrual Totals
September 30, 2006

Country	Study Families	Ineligible	Eligible
Australia	246	149	97
Canada	1230	722	508
Czech Republic	381	229	152
Estonia	80	48	32
Finland	928	518	410
Germany	266	155	111
Hungary	60	39	21
Italy	119	71	48
Luxembourg	13	7	6
Netherlands	125	72	53
Poland	214	129	85
Spain	127	69	58
Sweden	193	101	92
Switzerland	26	14	12
United States	939	560	379
	4947	***2883***	***2064***

HLA Eligible Randomized Subjects
By First Degree Relative with Type 1 Diabetes
September 30, 2006

	Parent(s) Only Parents with Type I Diabetes			Parent(s) & Sibling(s) Parents with Type 1 Diabetes					
Country	Mother Only	Father Only	Both	Mother Only	Father Only	Both	Sibling Only	No Relative Listed With Type 1 Diabetes	Total
Australia	48	36	2	0	0	0	11	0	97
Canada	274	158	6	6	5	0	58	1	508
Czech Republic	82	55	0	0	0	0	15	0	152
Estonia	17	8	3	0	0	0	4	0	32
Finland	146	217	2	0	7	0	38	0	410
Germany	54	29	4	0	2	0	22	0	111
Hungary	17	2	0	0	0	0	2	0	21
Italy	28	11	0	0	1	0	8	0	48
Luxembourg	5	1	0	0	0	0	0	0	6
Netherlands	23	19	0	0	3	0	8	0	53
Poland	55	7	2	0	1	1	18	1	85
Spain	36	17	2	0	1	0	2	0	58
Sweden	39	35	1	1	2	0	14	0	92
Switzerland	3	4	0	0	0	0	5	0	12
United States	186	95	5	4	9	0	80	0	379
	1013	***694***	***27***	***11***	***31***	***1***	***285***	***2***	***2064***