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A Finnish study shows for the first time that dietary intervention in infancy can prevent the initiation of the disease process leading to type 1 diabetes among high-risk children

A Finnish study published in the November 11, 2010 issue of the *New England Journal of Medicine* confirms the hypothesis that infant feeding plays a role in the initiation of the disease process leading to type 1 diabetes in children carrying increased genetic disease risk.

The study population comprised 230 newborn infants with at least one family member affected by type 1 diabetes and a predisposing genotype based on screening at birth from cord blood. The participants were randomized into two groups; the infants in the intervention group were weaned to a highly hydrolyzed casein-based formula (Nutramigen, Mead Johnson Nutrition), while those in the control group were weaned to a regular cow's milk-based formula supplemented with 20% Nutramigen to make the two formulas comparable in terms of smell and taste. The intention was that the participants should be exposed to their study formula for at least 2 months by the age of 6 months, or if exclusively breast-fed up to that age by the age of 8 months.

The study participants were observed up to the age of 10 years for the appearance of diabetes-predictive autoantibodies and progression to type 1 diabetes. Twenty-five children (12%) developed at least two diabetes-predictive autoantibodies out of five tested, which marks a high risk of presenting with clinical diabetes. Seventeen children tested positive for two or more autoantibodies had been randomized to the control group (16%), whereas seven belonged to the intervention (casein hydrolysate) group (7%). Nine children (8%) in the control group presented with clinical diabetes by the age of 10 years, while four of those (4%) who had been exposed to the casein hydrolysate progressed to clinical disease

Professor **Mikael Knip**, Hospital for Children and Adolescents, University of Helsinki, who has been responsible for the analyses of diabetes-predictive autoantibodies states that "the study showed that the safe and simple dietary intervention applied in this pilot trial was capable of reducing the emergence of diabetes-predictive autoantibodies by about 50% by age 10 in the participants carrying increased disease risk. The current study population does not provide sufficient statistical power to definitely conclude whether an intervention of this type will reduce the frequency of clinical type 1 diabetes, although the preliminary data are promising."

A full-scale trial – TRIGR (**T**rial to **R**educe **I**DDM in the **G**enetically at **R**isk) – was initiated in 2002 and is currently running in 77 study centers in 15 countries to provide a conclusive answer to the question whether weaning to a highly hydrolyzed formula will reduce the cumulative incidence of clinical type 1 diabetes. Two thousand one-hundred sixty children have been randomized for TRIGR. The first end-point in TRIGR, i.e. positivity for at least two diabetes-associated autoantibodies and/or

clinical type 1 diabetes by age 6, will be reached in 2013 and the final endpoint, clinical diabetes by the age of 10 in year 2017.

The current pilot trial and the full-scale TRIGR aim at primary prevention of type 1 diabetes, i.e. to stop the initiation of the disease process, which lasts for months and years before clinical disease manifestation. Dr. Knip emphasizes that the results indicate that it is possible to reduce the initiation of the disease process substantially by early dietary intervention in high-risk individuals. "On the other hand we have to keep in mind that this pilot trial has been performed in children with predisposing genes and a family member affected by type 1 diabetes. At this point it remains open whether this type of intervention will work in children from the general population," Dr. Knip said.

The researchers do not know what the decisive difference is between the casein hydrolysate and regular cow's milk-based formulas. An experimental study showed recently that a highly hydrolyzed formula reduces gut permeability and has a beneficial effect on gut microflora. Studies have been initiated to identify the mechanism(s) by which the highly hydrolyzed formula protects against beta-cell autoimmunity represented by diabetes-predictive autoantibodies. Another Finnish trial is currently testing the hypothesis whether an insulin-free formula decreases the initiation of the diabetic disease process in children at risk given the central role of insulin as an early autoantigen in type 1 diabetes.

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Professor Hans K. Åkerblom was the Principal Investigator for the current pilot trial, which was performed at the University of Helsinki, Helsinki University Central Hospital, University of Kuopio, University of Oulu, University of Tampere, University of Turku, Tampere University Hospital, National Institute for Health and Welfare and nine central hospitals, all in Finland. In addition, University of Toronto, Ontario, Canada, was involved in the study.

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