FOOD-CT-2005-007036

EARNEST

EARly Nutrition programming- long term follow up of Efficacy and Safety Trials and integrated epidemiological, genetic, animal, consumer and economic research

Instrument: Integrated Project

Thematic Priority 5.4.3.1: Food Quality and Safety

Final public report on activity 1.4.2

Title of activity: To study the synergistic influences of prebiotic oligosaccharides with other nutritional components on the early programming of atopic diseases

Start date of project: 15.04.2005 Duration: 5,5 Years

Organisation Name of Lead Contractor for this report: NUMICO

This activity was split into three parts. Two had been designed as follow-up studies on earlier (before EARNEST) nutritive interventions:

In study 1, Prof. Moro (Macedonio Melloni Hospital, Milan) and co-workers examined occurrence/absence of atopic disease in children with a parental history of allergy over a five year period after the children had received infant formula with GOS/FOS prebiotics in highly hydrolysed protein.

In study 2, Prof. Desager (Laboratory of Experimental Medicine and Pediatrics, University of Antwerp) and co-workers examined children at high risk for atopy, who were fed with infant formula with GOS/FOS/AOS prebiotics in highly hydrolysed protein.

In study 3, Prof. Hauner and Dr. Amann-Gassner (Klinikum Rechts der Isar, Munich) and coworkers tested for an influence of the n3/n6 ratio of nutritional fatty acids in the diet of pregnant women on the development of fat deposit tissues of their children (INFAT-Study).

Study 1: Neutral Prebiotic Oligosaccharides in the Prevention of Allergic disease and Infections

Introduction: A mixture of neutral prebiotics - short-chain galactooligosaccharides (scGOS) and long-chain fructooligosaccharides (lcFOS) – in formula taken by infants during the first 6 mo of life has been shown to reduce the incidence of atopic dermatitis (AD) and infectious episodes during the intervention period. The present study evaluated if these protective effects were lasting beyond.

Study design: In a prior prospective, randomized, double-blind, placebo-controlled design, healthy term infants with a parental history of atopy had been fed either a prebiotic-supplemented (scGOS/lcFOS) or placebo-supplemented (maltodextrin) hypoallergenic formula during the first 6 mo of life. Following this intervention period, blind follow-up continued until 2y of life. Primary endpoints were cumulative incidence of allergic manifestations. Secondary endpoints were number of infectious episodes and growth.

Results: Of 152 participants, 134 infants (68 in placebo, 66 in intervention group) completed the 2-year follow-up. During this period, infants in the scGOS/lcFOS group had significantly lower incidence of allergic manifestations. Cumulative incidences for atopic dermatitis, recurrent wheezing, and allergic urticaria were higher in the placebo group, (27.9, 20.6, and 10.3%, respectively) than in the intervention group (13.6, 7.6, and 1.5%) ($P < 0.05$). Infants in the scGOS/lcFOS group had fewer episodes of overall and upper respiratory tract infections ($P < 0.01$), fever episodes ($P < 0.00001$), and fewer antibiotic prescriptions ($P < 0.05$). Growth was normal and similar in both groups.

Preliminary results of the 5-year follow-up (80 completers to date; ~ 10 still expected) indicate persisting differences between both infant groups. Cumulative incidences for atopic dermatitis, recurrent wheezing, and allergic urticaria continued to be higher in the placebo group, (12.3, 12.2, and 16.3%, respectively) than in the intervention group (3.3, 6.7, and 3.3%) ($P < 0.05$).

Conclusions: Oligosaccharide prebiotics (scGOS/lcFOS) when started early in life have a protective effect against allergic manifestations and infections during the first 2 years of life. The protection against allergy-associated symptoms is still present at 5 years of life. The

long-lasting protection against allergy supports the hypothesis that the mixture should be acting through the modulation of the immune system.

Perspectives: Completion of the 5-year follow-up is expected to corroborate the preliminary results and to support the notion that prebiotics reduce the presence of allergic diseases.

Publications:
Arslanoglu S, Moro GE, Schmitt J, Tandoi L, Rizzardi S, Boehm G (2008) Early dietary intervention with a mixture of prebiotic oligosaccharides reduces the incidence of allergic manifestations and infections during the first two years of life. J Nutr 138: 1091-1095
Publication of the results of the 5-year-follow up is planned for 2010.

Study 2: Neutral and Acidic Prebiotic Oligosaccharides in the Prevention of Allergic Disease

Introduction: Emerging evidence suggests a link between the intestinal microbiota in infants and the development of atopic diseases. This study was designed to elucidate the role of the intestinal microbiota and prebiotics in relation to the development of allergic disease: eczema, allergic rhinitis and asthma.

Study design: 200 infants at high risk for atopy (parental history of atopy) were included from 2004 until 2006. Mothers were encouraged to breastfeed as long as possible. A nutritional intervention was performed in a double-blind, randomized, parallel manner from start of formula feeding until 1 year of age with a hypoallergenic formula with or without a mixture of neutral (scGOS/lcFOS) and acidic oligosaccharides (pAOS).
Faecal samples were collected at the age of 3 weeks, 6 months and 1 year. Parents completed questionnaires on diseases, possible complaints, feeding pattern and medication. Children were examined at the age of 1 year and 4 years.

Intermediate results: To date we can only provide preliminary data, because we decided to continue the study until the 6 year follow-up. At present, the study is still completely blinded. The children can only be assigned to one of the two nutrition groups by the investigators after unblinding the data set.

At the age of 1 year sensitization to food allergens was seen in 11%, sensitization to the inhalant allergen house dust mite in 2% and to both in 1% of the children (114 tested). At the age of 4 years 22% were tested positive to inhalant allergens, 4% to food allergens and 3% of the children to both (113 tested).

Perspectives: The unblinding, the analysis of the blood and faecal samples and the follow-up until the age of 6 years will contribute to answer the question: “Can prebiotics reduce the presence of allergic diseases?”

Publications: An abstract concerning the study was presented during the international conference of EARNEST (6th – 8th May, 2010, Munich, Germany). After unblinding, a publication in a scientific journal will follow.

Study 3 (INFAT-Study)
The Impact of Nutritional Fatty Acids During Pregnancy and Lactation for Early Human Adipose Tissue Development

Introduction: The INFAT-study tests whether a decrease of the n-6 versus n-3 fatty acid intake in pregnant and lactating women affects adipose tissue growth in newborns and might be a useful strategy for the prevention of childhood obesity.

Study design: 208 pregnant women living in Munich (southern Germany) were randomly allocated to one of two groups. The intervention group received fish oil capsules containing 1 g DHA and 300 mg EPA for oral intake between the 15th week of pregnancy and the 4th month after birth with the goal of shifting the dietary n6/n3-fatty acid ratio from 7:1 to around 3:1. The control group received recommendations for an adequate and healthy diet during pregnancy.
The infants adipose tissue mass was assessed with skinfold thickness measurements at 3 – 5 days, 6 weeks, 4 months, and 12 month after birth. For the differentiation of visceral versus subcutaneous fat mass ultrasonography and magnetic resonance imaging is used at 6 weeks and 4 months pp.
Secondary outcome parameters are adipokine and cytokine analysis in blood samples of mothers and children and in breast milk, fatty acid analysis in blood and milk samples and nutrient intake during pregnancy and lactation assessed by 7d dietary records.

Status: The enrolment of 208 pregnant women in the 15th week of gestation was successfully completed in July 2009. The follow-up rates at 6 weeks and 16 weeks after birth were 87% and 84% respectively. By the end of November 2009 all babies of the INFAT-study were born. The complete data set on perinatal outcome was available in December 2009 and analyses of birth outcomes, adverse events and baseline characteristics of the participants have been completed and presented in January 2010. By the end of March 2010 the collection of mother's blood samples and the analysis of the maternal biochemical parameters were finished.
The analysis of the fatty acid composition in a) blood samples & mother's milk and b) umbilical cord vessels has been conducted by a) Prof. Böhm and Dr. Bartke from Milupa GmbH and b) Prof. Decsi (University of Pécs). So far, Milupa has analysed 79% of all plasma samples, 65% of all red blood cells and 100% of the breast milk samples. Analysis of the fatty acid profile in plasma phospholipids (PL) and red blood cells (RBC) of the blood samples of the mothers and their infants will be finished by Milupa in October 2010. Analysis of fatty acid composition in umbilical cord vessels has been completed in Mai 2010. We now have data on the fatty acid composition of n=125 umbilical cord veins and arteries available (control group: n=61; intervention group: n=64).

Intermediate results: The duration of pregnancy was 4 days longer in the intervention group (280 days) compared to the control group (276 days) ($p<0.05$). This is in accordance with other studies supplementing n-3 fatty acids during pregnancy. Accordingly, the birth weight of newborns was significantly higher in the intervention group (3534 g) vs. the control group (3356 g) ($p<0.05$). As expected and also confirmed by other studies, triglycerides increased significantly less during pregnancy in the intervention group (15th week: 102 mg/dl, 32nd week: 177 mg/dl, n=101, $p<0.05$) compared to the control group (15th week: 112 mg/dl, 32nd week: 217 mg/dl, n=102). Together with the significant increase in DHA and EPA plasma levels in the intervention group, but not the control group (data not shown), these results strongly confirm, that the intervention with the fish oil capsules was successful. As a second part of the intervention and important contribution to the high compliance, the dietary counselling with the intention of a normalisation of arachidonic acid intake within the

intervention group worked well according to preliminary analyses (significantly lower intake of arachidonic acid intake in the intervention group compared to the control group).

Perspectives: Final results depend on the completion of the biochemical analyses.

Publications: Publications of the results in a scientific journal will follow by the end of 2010.