Metabolic Programming, Breastfeeding And Later Risk Of Obesity

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Abstract

Nutritional sciences have found a new perspective of nutrition in recent years when it became clear that nutritional deficiencies may have long-term consequences even if treated and corrected in later life. Critical life periods were identified- like infancy and early childhood or the prenatal period where nutrition plays a special role producing a so called programming effect- long-term metabolic effect which affects health and development. The association of early malnutrition with diseases in adulthood was first indicated by Barker et al. who described the increased frequency of diabetes type 2 and cardiological problems in those adults who were born with low birth weight. Since then many other arguments were found- numerous studies indicated protective effect of breast feeding on obesity risk, arterial hypertension, diabetes or stimulation of cognitive development. The Barker hypothesis has been developed and it was shown that not only low birth weight but catch up growth could play a role in producing cardiological risk in adult life. Our team contributed to the generation of data showing that high protein intake in infancy increases BMI at the age of 2 and 6 years. We also tried to explain the metabolic programming effect by stimulation of IGF-1 axis. Numerous other factors seem to be involved in the programming effect such as microbiome programming in relation to the role of intestinal microflora. In this paper we refer mainly to the concept of metabolic programming of obesity.

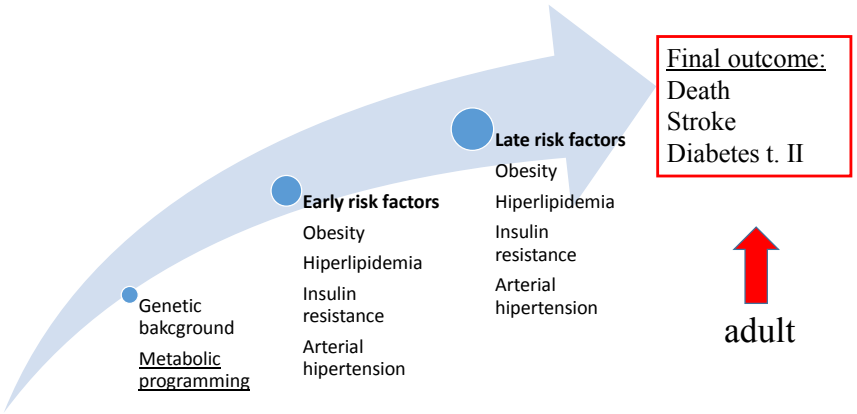
Introduction

The increasing incidence of obesity, cancer, cardiac problems, diabetes, allergy and autoimmune diseases in recent years may be explained by unhealthy life style in adulthood, hygiene hypothesis etc. However there is growing evidence that environmental factors in early life could already affect adult health. Numerous studies looked at associations of early nutrition and nutritional status with later health problems without bringing the direct proof of the cause-effect association. **The processes by which disease risk is regulated remain to be elucidated. Different organ systems have their own critical periods of development. Thus, short-term and long-term consequences may differ depending on the time point of nutritional intervention and organ specific responses.** In recent years several randomized controlled studies were performed to check the role of different nutrients or diets on risk of various diseases and confirmed the hypothesis of so called programming effect.

Barker hypothesis

The first evidence on the association of early nutrition with later health was described by Barker et al. who showed an increased frequency of diabetes type 2 (TD2) and cardiovascular diseases in adults born with low birth weight. The Barker hypothesis tries to explain the mechanism of programming of cardiovascular risk and relates it to fetus malnutrition resulting in chronic stress in fetal life affecting glucocorticoid release and altered intrauterine growth. Low birth-weight seems to lead to increased fat deposition in the situation of energy excess in adults as well as decreased muscle mass, decreased numbers of nephrons, hepatocytes and Langerhans islets cells. Both genetic background and a programming effect of early nutrition seem to contribute to the development of cardiovascular risk factors with an expected clinical outcome of cardiovascular disease and TD 2 (fig.1).

Fig. 1: Final outcome is related to genetic background and metabolic programming



The Barker hypothesis which focused on prenatal life. has been later completed with data showing additional effect of neonatal nutrition. Catch up growth in infants born with low birth weight seems to be the major factor involved in programming of later disease risk. Shingal et al. in a randomized trial showed that high protein and high energy diet improves growth in infants but increases risk of obesity, diabetes and high blood pressure in childhood.

Breastfeeding

Breastfeeding is the golden standard of nutrition in infancy. Numerous studies have shown an association between breastfeeding and a decreased risk of obesity and other disorders in later life, as compared to infant formula feeding. Some of the studies have shown better neurodevelopment in breastfed children, but other confounding factors musts always be taken into consideration. PROBIT study which was conducted in Belarus, showed that a breastfeeding promoting educational intervention resulted in better neurodevelopment at the age of 6 ½ years. The same study did not confirm a significant influence on obesity risk at the age of 6 ½ years. However a recent WHO report from 2013 including meta-analysis of 75 observational studies demonstrated a positive effect of breast feeding on obesity prevention. Early breastfeeding was also protective against the risk of type 2 obesity. A meta-analysis published in 2005 showed, that breastfeeding also decreased blood pressure later in life.

Programming effect of proteins

Several factors might be involved in early programming of later obesity risk. We proposed high protein intake with formula feeding as a major causal factor. Our hypothesis was built on earlier observations reporting that dietary protein intakes modulate blood concentrations of insulin-like growth factor-1 (IGF-

1). The IGF-1 axis was shown to regulate early growth, adipose tissue differentiation and early adipogenesis in animals and in humans. The most sensitive window for programming effects is still uncertain and has been proposed to last from the first weeks up to the first 2 years of life, since weight gain both in infancy and in the second year of life have been demonstrated to impact on later obesity risk. We tested this hypothesis in the European Childhood Obesity Project (CHOP) Trial, a randomized double blind trial where infants were assigned either to conventional formula feeding with a relatively high protein supply during the 1st year of life, or to a protein reduced intervention formula with equal content of energy achieved by adjustment of total fat content, and similar content of other nutrients. Feeding conventional formula in the first year induced faster weight gain and BMI up to 2 years without any difference in length growth, compared to feeding with reduced protein formula or breast-feeding Data from the follow-up at 6 years of age confirmed the programming effect of nutritional intervention in the 1st. year of life.

In the CHOP study, we found consistent changes in biochemical and endocrine markers which fit the hypothesis of metabolic programming of obesity: increased plasma levels of non-essential amino acids, especially branched chain amino acids in infants fed the higher protein diet in association to increased concentrations of total and free IGF-1, increased urinary C-peptide levels (reflecting increased insulin secretion) and lower serum glucose levels. Compared to formula-fed children, breastfed children had generally lower plasma amino acid levels, a less active IGF-1 axis and lower insulin production.

Anthropometric parameters, such as body mass index (BMI) and IGF-1 were correlated in the first 6 months of life suggesting a possible role of IGF-1 axis in obesity programming. We analyzed also genetic regulation of IGF-1 secretion and were able to show a predominant nutritional regulation of the IGF-1 axis compared to the small influence of single nucleotide polymorphisms.

Early protein intake has an impact on kidney function during the first year of life. Formula-fed children, with higher protein intakes had larger kidney volumes measured by ultrasound at 6 months of age, higher serum urea concentration and urea/creatinine ratio. Larger kidney size seems to be partly explained by a significant effect of free IGF-1 on kidney volume. Thus, IGF-1 is involved in protein-induced kidney growth in healthy infants. Since, the number of nephrons is relatively constant from the 36th week of gestation onward, we speculate that the volume of nephrons rather than their number is responsible for the increase in kidney volume. Whether the kidney volume will normalize with later diet changes is still unknown. Increased kidney size was previously shown to be the first symptom associated with later hyperfiltration and nephropaty in obesity and in diabetic nephropathy. Some authors also suggest a positive association between kidney volume and blood pressure. It seems that early diet may influence kidney development and function. Long term follow up of the same cohort is necessary to check if the observed changes persist into adolescence and adulthood. The children are currently being evaluated at the age of 11 years as part of a wider project:' Long term effects of early nutrition on later health', called Early Nutrition.

Microbiome programming

The programming effect of nutrition seems to be related not only to metabolism of nutrients but also to intestinal microflora. Randomized trials are lacking but some interesting observations are linking

microflora in infancy with later obesity risk. Kaliomakki et al. found that an increased number of bifidobacteria and a decreased number of Staphylococcus aureus in infancy is associated with a lower obesity risk in 7y old children. Throughout infancy, the composition and the diversity of the gut microbiota change under the influence of external factors. Breastfeeding has a great influence on microflora development- Bifidobacterium-dominated microbiotas are more frequent in breastfed babies than among infants fed with formula. By one year of age, the microbiota of infants substantially resembles that of the adult, being dominated by the phyla Bacteroidetes and Firmicutes. Cesarian section is another factor strongly correlated with microflora changes.

Cesarian section and long-term disease risk

Cesarian section enhances several risks such as, prematurity, difficulty for breastfeeding and indirectly occurrence of infectious diseases. The association of cesarian section with allergy is still being discussed. Since many papers that report an increased risk of obesity are based on cohort studies, the evidence is limited. A big cohort of 2.063 young adults aged 23 to 25 years in Brazil was studied. An increased risk of obesity relying on increased waist circumference [RR 1.22 (95%CI 1.07-1.39)] was shown to be associated with cesarian section, and remained significant after correcting for confounding factors. Another cohort from Brasil showed an increased risk of obesity related to cesarean section of 50% at the age of 4, 11 and 15 years but not at the age of 23 years. In this study, the risk was not anymore significantly different after correcting for other factors. The influence of cesarian section on obesity risk remains an open question.

Summary

Metabolic programming is a new scientific concept explaining the association of early nutrition with later health outcomes. Most of the data is based on observational studies. Several recent intervention trials provided strong evidence of programming effects. Mechanistic studies which try to explain mechanisms of programming are very challenging. Current understanding of these early and late occurring events is still very limited.

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Piotr Socha

Piotr Socha is a Head of the Gastroenterology, Hepatology and Nutrition Disorders Ward in The Children's Memorial Health Institute in Warsaw.

His research and clinical work were devided into two streams- nutrition and liver. He described nutritional problems in cholestatic liver disease-eg. he developed the concept of TPGS (water soluble vitamin) therapy, indicated the risks and causes of LCPUFA deficiency. His research concentrated also on non-alcoholic fatty liver disease with critical approach to therapy. His clinical experience with rare diseases brought to scientific contribution in research on Wilson disease and newly described PGM-1 as a defect of glycosylation. Most of the recent research work was devoted to obesity prevention and therapy and feeding disorders became one of the major clinical interests.

Piotr Socha was the chair of the Hepatology Committee of ESPGHAN (2010-2013). He was awarded with John Harries Prize by ESPGHAN in 1995. Piotr Socha contributs/contributed to 7 EU projects (CHOP, EUROWILSON, EARNEST, PERFECT, NUTRIMENTHE, TOYBOX, EARLY NUTRITION). He is the president of the Polish Society for Pediatric Gastroenterology, Hepatology and Nutrition. He published over 250 peer reviewed papers and contributed to 26 books. He is the Associated Editor of the Journal of Pediatric Gastroenterology, Hepatology and Nutrition.

The major research interests at present are childhood obesity and its complications (mainly non-alcoholic fatty liver disease), feeding disorders, immune deficiencies causing severe inflammatory bowel disease, Wilson's disease, congenital defects of glycosylation and gene modifiers in those frequent and rare diseases.

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