Infant Feeding and Later Obesity Risk

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Abstract Some 30 years ago, Günter Dörner proposed that exposure to hormones, metabolites and neurotransmitters during limited, sensitive periods of early development exert programming effects on disease risk in human adults. Early programming of long term health has since received broad scientific support and attention. For

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example, evidence increases for programming effects of infant feeding choices on later obesity risk. Meta-analyses of observational studies indicate that breast feeding reduces the odds ratio for obesity at school age by about 20%, relative to formula feeding, even after adjustment for biological and sociodemographic confounding variables. We hypothesized that breast feeding protects against later obesity by reducing the likelihood of high weight gain in infancy, and that this protection is caused at least partly by the lower protein supply with breast milk relative to standard infant formulae (the "Early Protein Hypothesis"). These hypotheses are tested in the European Childhood Obesity Project, a randomized double blind intervention trial in more than 1,000 infants in five European countries (Belgium, Germany, Italy, Poland, Spain). Formula fed infants were randomized to receive during the first year of life infant formulae and follow-on-formulae with higher or lower protein contents. Follow-up at 2 years of age shows that lower protein supply with formula normalizes early growth relative to a breast fed reference group and to the WHO growth reference. These results demonstrate that modification of infant feeding practice has an important potential for long-term health promotion and should prompt a review of the recommendations and policies for infant formula composition.

Keywords Infant protein requirements • infant growth • insulin • insulin like growth factor I (IGF1) • metabolic programming • randomized clinical trial

Abbreviations BMI: body mass index; IGF1: insulin like growth factor 1; ROC: receiver operating curves; YI: Youden Index

1 Introduction

Evidence accumulates that metabolic events during critical time windows of pre- and postnatal development have marked modulating effects on health in later life, a concept often referred to as *programming* or *metabolic programming* (Koletzko et al. 2005a). The term *programming* was first used in this context in the scientific literature by Professor Günter Dörner, former head of the Institute of Experimental Endocrinology at the Charité Hospital, Humboldt University at Berlin, Germany, more than 30 years ago (Koletzko 2005). He concluded that the concentrations of hormones, metabolites and neurotransmitters during limited, sensitive periods of early development can pre-programme brain development and functional disorders in human adults, as well reproduction and metabolism (Dörner 1975). At that time Dörner also proposed an interaction between the genetics and environment during early development in determining later health outcomes in adulthood, a concept that only recently has been confirmed by experimental data (Koletzko et al. 2005; Schmidt et al. 2000; Ozanne et al. 2004; Plagemann 2004). This concept of early developmental plasticity has gained wide popularity following epidemiological studies documenting relationships between early markers of growth and the later risks of hypertension, diabetes and coronary heart disease

in adulthood (Barker et al. 1989; Singhal and Lucas 2004; Cole 2004; Tu et al. 2005). Growth patterns in the first year of life are receiving increased attention since rapid weight gain in infancy has been associated with adverse later health outcomes (Koletzko et al. 2005; Metcalfe and Monaghan 2001), such as higher blood pressure (Bansal et al. 2008), higher rates of overweight and body fat deposition (Toschke et al. 2004; Wells 2007; Stettler 2007; Singhal and Lanigan 2007) and higher rates of diabetes (Dunger et al. 2007).

Since infant growth patterns can be modified by infant feeding practices, prospective controlled intervention trials are needed the explore the preventive potential of optimizing early nutrition for long term health, well-being and performance. If successful, such preventive interventions could markedly enhance the possible improvement of quality of life of populations, and also have a large economic benefit for societies. Therefore, major investments in research are justified to explore the effects of interventions on relevant outcomes, the effect sizes that can be achieved, and the underlying mechanisms of such early nutritional programming. A randomized controlled trial is currently being performed as part of the European Early Nutrition Programming project (www.metabolic-programming.org), to explore the effects of modified infant formula composition on the rate of early weight gain and later obesity risk.

2 Infant Feeding and Programming of Later Obesity Risk

Childhood obesity is considered a global epidemic in view of the alarming increase in its prevalence and severity, not only in affluent but also in less privileged childhood populations worldwide (Koletzko et al. 2002a, 2004; Fisberg et al. 2004). Childhood obesity has very serious short and long term consequences on quality of life, performance achieved, as well as long-term health and life expectancy. The obesity epidemic is expected to create huge costs for society due to both loss of productivity and to ensuing costs for health care and social security systems. Therefore, effective therapeutic intervention in obese children is needed, but results of available treatment concepts are less than satisfactory, and costs tend to be high (Koletzko 2004). A Cochrane review on interventions for treating obesity in children found that no conclusions on the effects of treatment strategies and their components can be drawn with confidence (Summerbell et al. 2004). Therefore, more emphasis must be put on the development, evaluation and implementation of effective primary prevention of obesity, where optimized infant feeding may be one important element that offers opportunities for contributing to prevention of later obesity risk (Koletzko et al. 2005).

2.1 Early Growth and Later Obesity Risk

McCance and Widdowson showed in the 1950s that alteration of early growth in animals by manipulation of food intake during sensitive periods of early development predetermined the animals' ultimate weight in adulthood (Ashwell 1993). In humans high birth weight has been proposed as a risk factor for later overweight (Binkin

et al. 1988; Eriksson et al. 2003), which could reflect both the roles of genetics and of early priming by the intrauterine environment. Additionally, recent studies pointed to further priming of childhood overweight in the first 2 years of life by a high postnatal weight gain (Ong et al. 2000; Stettler et al. 2002, 2003, 2005; Chomtho et al. 2008).

We evaluated growth measures of some 4,235 German children aged 5 to 6 years who participated in the obligatory school entry health examination in the state of Bavaria, and for whom data on early weight, length, BMI and Ponderal Index evaluation were available based on measurements obtained at birth, 6, 12 and 24 months as part of the preventive health care checks offered to all children free of charge (Toschke et al. 2004). Overweight at school entry was assessed according to sex- and age-specific BMI cut-points. Growth measures in early life were analysed as possible predictors of later overweight by receiver operating curves (ROC) and predictive values. For all parameters the highest areas under ROC were observed for the gain between birth and 24 months. The area under ROC decreased in the order from weight gain (0.76) to BMI gain (0.69) to length gain (0.58) ($p < 0.001$) (Table 1). Thus, high weight gain during the first 24 months is the best overall predictor of overweight at school entry compared to other anthropometric markers and time intervals.

Similar to our findings, numerous studies in other populations also found rapid weight gain during infancy or the first 2 years of life associated with an increased

Table 1 Area under receiver operating characteristic (ROC) curves and cutpoints, sensitivity and specificity at highest Youden index for early anthropometric measurement prediction of overweight at school age in 4,235 children in Bavaria, Germany. Weight gain from birth to age 2 years is the best predictor of overweight at school age (Adapted from Toschke et al. 2004)

Measure	Area under ROC	Cutpoint at highest Youden index (YI)[†]	Sensitivity at highest YI	Specificity at highest YI
Age 0–6 months				
Weight	0.63 (0.60–0.66)	5,100 g (19)	45 (40–50)	74 (73–76)
Length	0.51 (0.48–0.55)	20 cm (4)	21 (17–25)	83 (81–84)
BMI[‡]	0.60 (0.57–0.63)	5 (15)	43 (38–48)	72 (70–73)
Ponderal index[§]	0.59 (0.53–0.60)	0.2 (11)	32 (27–37)	78 (76–79)
Age 0–12 months				
Weight	0.68 (0.65–0.70)	6,933 g (27)	68 (63–72)	59 (58–61)
Length	0.55 (0.52–0.58)	26 cm (9)	66 (61–71)	43 (42–45)
BMI[‡]	0.63 (0.60–0.66)	4 (20)	66 (62–71)	53 (51–55)
Ponderal index[§]	0.57 (0.54–0.60)	−0.3 (11)	64 (59–69)	47 (45–48)
Age 0–24 months				
Weight	0.76 (0.74–0.79)	9,764 g (41)	70 (65–75)	71 (69–72)
Length	0.58 (0.55–0.61)	39 cm (13)	45 (40–50)	68 (66–69)
BMI[‡]	0.70 (0.67–0.72)	4 (31)	57 (52–62)	74 (73–75)
Ponderal index[§]	0.61 (0.58–0.64)	−0.5 (17)	44 (39–49)	72 (71–74)

Data are given as value (95% confidence interval) unless otherwise indicated.

[†](Sensitivity + specificity) − 1.

[‡]Calculated as weight in kilograms divided by the square of height in meters.

[§]Calculated as weight in kilograms divided by the length in meters cubed.

risk of later obesity. Three recent systematic reviews on the available evidence from the large number of observational studies confirmed that rapid weight gain in infancy and the first 2 years of life is a significant risk indicator for later adiposity (Baird et al. 2005; Monteiro and Victora 2005; Ong and Loos 2006). Thus, early infancy may provide an opportunity for interventions aiming at reducing later obesity risk.

3 Protective Effects of Breast Feeding Against Later Obesity

Populations of infants fed breast milk or formula show slightly different growth, with formula fed infants showing higher body weight at the end of the first year of life (Kramer et al. 2004). Based on a systematic review of 19 studies in affluent populations, Dewey concluded that the cumulative difference in body weight amounts to approximately 400 g less weight by the age of 12 months in infants breast-fed for 9 months, and as much as 600–650 g less weight at 1 year in infants that are breast-fed for 12 months (Dewey 1998). In view of this large effect of the mode of feeding on early weight gain, we aimed at studying whether breast feeding might also confer protection against later obesity risk.

In a cross sectional survey in Bavaria, Germany, we assessed the impact of breast feeding on the risk of obesity and the risk of being overweight in children at the time of entry to school (von Kries et al. 1999). Data collected on height and weight of 134,577 children participating in the obligatory health examination at the time of school entry in Bavaria were used to calculate body mass index (BMI) values, and the 90th and the 97th centile values of German children aged 5 and 6 years were calculated and served as the cutoffs to define overweight and obesity, respectively. In a subsample of 13,345 children, early feeding, diet, and lifestyle factors were assessed using responses to a questionnaire completed by parents, and data of 9,357 children aged 5 and 6 who had German nationality were included in the final analysis. Children who were never breast fed had a higher prevalence of both overweight (12.6% vs. 9.2%) and of obesity (4.5% vs. 2.8%) than children who had been breast fed. Longer duration of breast feeding was associated with a lower prevalence of later obesity: obesity prevalence was 3.8% for 2 months of breast feeding, 2.3% for 3–5 months, 1.7% for 6–12 months, and 0.8% for more than 12 months. Similar relations were found with the prevalence of being overweight. The protective effect of breast feeding was not attributable to differences in social class or lifestyle, but remained significant after adjusting for confounding factors. Compared to children who were never breastfed, those who had ever been breastfed showed a significantly reduced adjusted odds ratio for overweight (0.79, 95% confidence interval 0.68–0.93) and obesity (0.75 [0.57–0.98]). We also found an inverse dose–response relationship between duration of breastfeeding and prevalence of overweight and obesity (Fig. 1), which is compatible with a causal effect of breast feeding or breast milk components on obesity reduction.

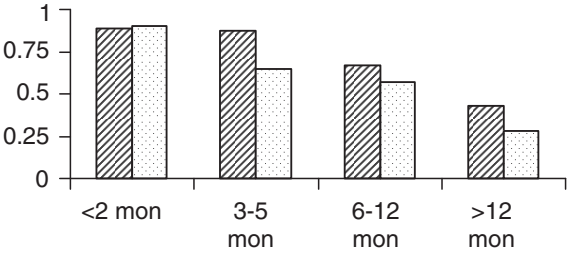

Fig. 1 Duration of breast-feeding in infancy (months) is inversely related to the odds ratio (adjusted for confounding factors) for overweight (striped bars) and obesity (light bars) at school entry in 9,357 German children (Adapted from von Kries et al. 1999)

Following our publication, many other investigators around the world evaluated the relation between breast feeding and later obesity in data collected from various cohort studies around the world. This allowed us to perform a systematic review and meta-analysis of published epidemiological studies (cohort, case-control or cross-sectional studies) evaluating effects of early feeding-mode on later overweight and obesity (Arenz et al. 2004). We limited studies to those who adjusted for at least three of the relevant confounding or interacting factors birth weight, parental overweight, parental smoking, dietary factors, physical activity and socioeconomic status. We accepted parental education as an appropriate indicator of socioeconomic status. Other inclusion criteria were: comparable risk estimates as OR or relative risk had to be reported and age at the last follow-up had to be between 5 and 18 years; feeding-mode had to be assessed and reported and obesity as outcome had to be defined by body mass index (BMI) percentiles 90, 95 or 97 to allow for comparison of the studies. We did not require all studies to use identical reference values. If risk estimates were calculated for different percentile values in a particular study, the estimate for the highest percentile-value was included in the meta-analysis. Electronic databases were searched and reference lists of relevant articles were checked. Calculations of pooled estimates were conducted in fixed-effects and random-effects models. Heterogeneity was tested by Q-test. Publication bias was assessed from funnel plots and by a linear regression method. Nine studies with more than 69,000 participants met the inclusion criteria. The meta-analysis showed that breast-feeding reduced the risk of obesity in childhood significantly. The adjusted odds ratio was 0.78 (95% CI [0.71, 0.85]) in the fixed-effects model (Fig. 2). The assumption of homogeneity of results of the included studies could not be refuted (Q-test for heterogeneity, $p > 0.3$), stratified analyses showed no differences regarding different study types, age groups, definition of breast-feeding or obesity, and number of confounding factors adjusted for. A dose dependent effect of breast-feeding duration on the prevalence of obesity was reported in four studies. Funnel plot regression gave no indication of publication bias.

Similar results were obtained by Harder and coworkers a year later in a meta-analysis with different inclusion criteria and a much larger number of evaluated studies (Harder et al. 2005). They concluded that ever breastfeeding leads to significantly reduced pooled adjusted odds ratio for later obesity of 0.75 (95% CI: 0.68–0.82), and again they found a clear dose–response effect, with each

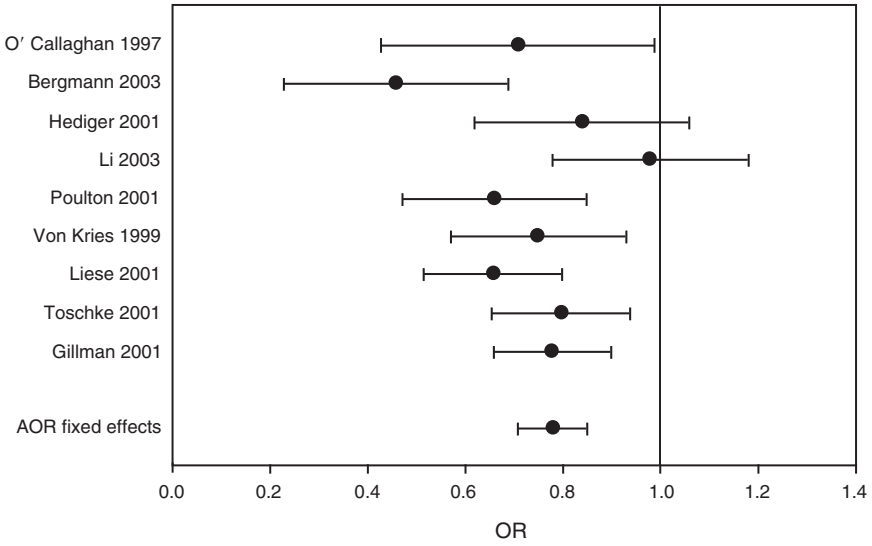

Fig. 2 Forrest plot of meta-analysis of effects of breast feeding versus formula feeding on childhood obesity: covariate-adjusted odds ratios of nine studies and pooled adjusted odds ratio (Adapted from Arenz et al. 2004)

additional month of breast feeding reducing later obesity risk by a further 4%. A further meta-analysis published thereafter also confirmed a protective effect of breast feeding, but reported a smaller effect size with an odds ratio of 0.87 (Owen et al. 2005). This result was primarily due to the data of one publication based on the population of the Women, Infants and Children program in the USA (WIC) supporting low-income women and children, which contributed 75% of the total weight of all studies, and the question has been raised whether specific aspects in this cohort such as a high degree of mixed feeding might explain these results. One cluster randomized study performed in Belarus had randomized hospitals to a program of breast feeding intervention or no active intervention, and it achieved a significantly longer duration of breastfeeding with the intervention (Kramer et al. 2007). When the children were revisited at the age of 6.5 years, measures of obesity in the intervention and control groups were not significantly different. However, in this study basically all children had been breastfed, and while the intervention modified the duration of breastfeeding the study does not allow conclusions on the effect of breast versus formula feeding. Moreover, the prevalence of obesity was rather low in this population, and the overall power of the study to detect effects on obesity is not high.

The consistent finding of a modest but significant protective effect of breastfeeding on later obesity in numerous observational studies and in three meta-analysis is encouraging and may contribute to promoting, protection and support of breastfeeding. However, it appears worthwhile to elucidate the potential underlying

mechanisms for protection by breastfeeding because this would strengthen the conclusions on apparent protective effects, and it might help to extend protective effects to populations of infants that are not benefiting from long duration of full breastfeeding.

4 Potential Causative Mechanisms for the Protective Effects of Breast Feeding on Later Obesity

A number of hypotheses could be raised with respect to potential causes for a protective effect of breast feeding on later obesity risk. Even though the inverse relationship of both breast feeding and breast feeding duration with later obesity was shown to persist in many studies after adjustment for measurable confounding variables, residual confounding cannot be fully excluded. Since healthy babies can generally not be randomised to breastfeeding or formula feeding for ethical and practical reasons, undisputable proof for a causal protective effect of breastfeeding is difficult to obtain. However, the consistent results of many studies and the dose–response relationship between longer duration of breast feeding and greater later reduction of obesity risk observed in a number of studies make it likely that there is a causal effect of breast feeding.

4.1 Differences in Behaviour

Differences in feeding behaviour and mother–child-interaction between populations of breast and formula fed infants might play a role. Breast fed infants show a different suckling pattern and a higher suckling frequency (Mathew and Bhatia 1989; Bosma et al. 1990). Breast fed infants seem to have greater degree of control on meal sizes and intervals than infants fed formula. Sievers and coworkers monitored marked differences in feeding patterns, with a 20–30% higher feeding volume in formula fed infants after 6 weeks of life as well as a smaller number of total meals and of nightly meals in bottle fed babies at 4 months of age (Sievers et al. 2002). Such early differences in feeding behaviour might be related to later body size. Agras and coworkers reported that early feeding patterns were predictive of body mass index at 3 years of age, with high-pressure sucking measured in the laboratory at 2 and 4 weeks of age (denoting a vigorous feeding style) associated with greater degree of adiposity in toddlers (Agras et al. 1990).

In contrast to infant formula, breast milk shows marked variation in its composition, taste and smell from day to day, and even from meal to meal, depending on maternal dietary habits and other metabolic factors, as well as duration of lactation, the volume of milk consumed and the degree of breast expression (Rodriguez et al. 1999). Since early taste experience in infancy has been reported to favour later consumption of foods with the same taste (Mennella et al. 2001), it is conceivable

that breast fed infants might be programmed to different food selection and dietary habits in alter life.

Breastfeeding is believed to enhance emotional bonding of the mother to her child, mediated in part by the stimulation of maternal oxytocin release by infant suckling, and breastfeeding mothers have decreased neuroendocrine response to stressors, increased parasympathetic nervous system modulation, lower perceived stress levels and fewer depressive symptoms (Klaus, 1998; Mezzacappa, 2004). These effects of breast feeding might well have repercussions on the interaction between mother and child and health related behaviours. These and further behavioural hypotheses are plausible and attractive, and they deserve further exploration, even though experimental testing of these hypotheses may not be easy.

4.2 Differences in Milk Composition

While the mode of feeding an infant at the breast cannot be copied with bottle feeding of human milk substitutes, some of the compositional differences and substrate supply between breastmilk and infant formula might potentially be reduced by appropriate modifications of infant formula composition. Promising hypotheses can be deduced from studies evaluating physiological responses of breast and bottle fed infants. We hypothesized that the higher rates of weight gain in populations of formula fed infants, as compared to infants fed human milk, are at least partly due to differences in metabolizable protein intakes (Koletzko et al. 2005).

Infant formulae tend to have a higher average caloric density (kcal/100 ml) than average values for breast milk, and energy supplies per kg bodyweight between 3 and 12 months of age are 10–18% higher in formula fed infants than in breastfed babies (Heinig et al. 1993). However, much greater is the difference in protein intake per kg bodyweight, which is 55–80% higher in formula than in breast fed infants (Fig. 3) (Alexy et al. 1999). In rats, prenatal high protein exposure decreased energy expenditure and increased later adiposity (Daenzer et al. 2002), and a high postnatal protein and nutrient supply led to higher adult body fat deposition (Kim et al. 1991) and increased adult weight by 10–40% (Jones et al. 1984). A high protein intake in excess of metabolic requirements may enhance the secretion of insulin and insulin like growth factor 1 (IGF1) (Fig. 4). Infants fed cows' milk protein based infant formula were shown to have far higher postprandial levels of insulin on day 6 of life than breastfed infants (Lucas et al. 1981). High insulin and IGF1 values can enhance both growth during the first 2 years of life (Karlberg et al. 1994; Hoppe et al. 2004a) as well as adipogenic activity and adipocyte differentiation (Hauner et al. 1989) (Fig. 4). High protein intakes may also decrease human growth hormone (hGH) secretion and lipolysis. Some epidemiological studies showed a significant relationship of high protein intakes in early childhood, but not of the intakes of energy, fat or carbohydrates, to an early occurrence of the adiposity rebound and to a high childhood body mass index (BMI), corrected for parental BMI (Rolland-Cachera et al. 1995;

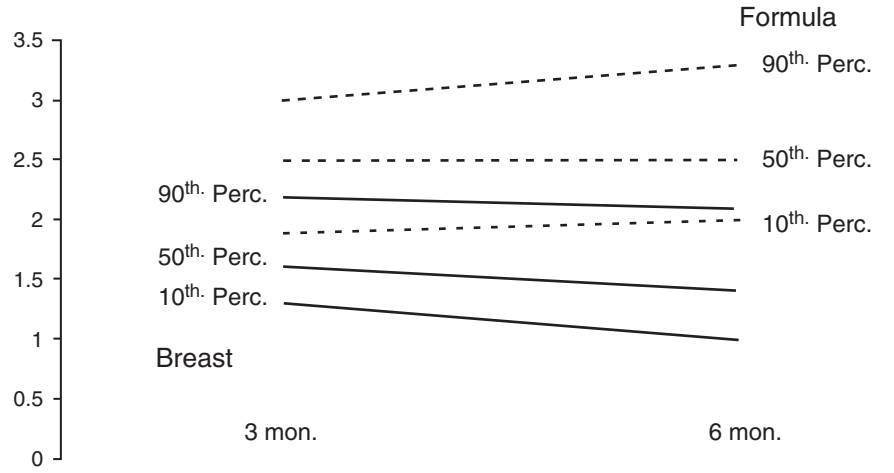

Fig. 3 Percentiles of protein intake (g/kg and day) of healthy breastfed and formula fed infants at the ages of 3 and 6 months (median and 90th/10th percentiles). Data of the German DONALD study (Redrawn from data of Alexy et al. 1999)

Parizkova and Rolland-Cachera 1997; Scaglioni et al. 2000; Hoppe et al. 2004b). These and other data support our hypothesis that a higher protein intake with infant formula than provided with breast milk and in excess of metabolic requirements may predispose to an increased obesity risk in later life (the Early Protein Hypothesis) (Koletzko et al. 2005).

5 Testing the Early Protein Hypothesis: The European Childhood Obesity Project

In addition to prospective epidemiological and experimental studies, human intervention trials are needed to test the "Early Protein Hypothesis". The European Childhood Obesity Project (www.metabolic-programming.org) funded by the European Commission's fifth Framework Research Programme and sixth Framework Research Programme was set up to test, in a randomized double blind intervention trial, whether higher or lower protein intakes during the first year of life influence growth until the age of 2 years and obesity risk at school age. This trial is conducted in five European countries (Belgium, Germany, Italy, Poland, Spain) which differ substantially in the practice of infant and young child feeding and in their prevalence of adult obesity. Therefore the trial offers the opportunity to combine a multicentre intervention trial on infant formulae which differ in their balance of protein and fat (provided by Bledina, Steenvoorde, France), with an epidemiological observation study which can assess protein intake in the overall early diet. We anticipate that this approach will enable us to assess the effects of

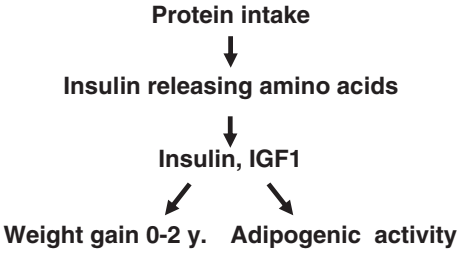

Fig. 4 High protein intakes with infant formula may induce high circulating concentrations of insulin releasing amino acids, which may stimulate the secretion of insulin and insulin like growth factor 1 and hence induce both an enhanced weight gain from birth to 2 years of life as well as enhanced adipogenic activity

variables which differ substantially within Europe, as well as to assess the effects of the randomized controlled intervention. The inclusion of a group of breastfed infants in each centre will also allow an epidemiological comparison of the effects of breastfeeding and formula feeding.

Growth from birth to age 2 years, a marker of later obesity risk, was chosen as the primary outcome variable, based on our previous findings that this is a predictive marker of later obesity risk (Toschke et al. 2004). In addition, a variety of further variables are measured, including detailed data on diet, lifestyle and behaviour, biochemical and endocrine markers, markers of renal function, and others. Randomisation and data collection are performed via the internet based on uniform electronic case report forms, using specially developed information technology architecture with a central database and 12 remote data entry stations as well as dedicated software that allows for secure data protection. Mechanisms for quality assurance have also been established. Data input and transfer to the central database are supervised by a contract research organization participating in the project.

Recruitment for the intervention and follow-up until the age of 2 years has been successfully completed. The first data evaluation indicates that the group of infants randomized to the formulas with higher protein contents show a significantly higher body weight and body mass index at the age of 2 years than the group of infants randomized to lower protein supply (Koletzko et al. submitted 2008). Provision of the lower protein content with formula led to normalized growth measures at 2 years, relative to the breast fed reference group. Further data evaluation is ongoing, and the subjects in the trial are being followed up to explore both the longer-term safety as well as the potential benefits of the intervention at preschool and school age. Based on the available data from observational trials, we expect that the reduction of weight for length achieved at 2 years with the lower protein supply may reduce later obesity risk by some 10–15%. However, even the early results obtained might lead to a review of recommendations for infant feeding, policy and regulatory guidance, as well as product design, since the aim is for physiological growth of formula fed populations similar to the growth of healthy breastfed populations (Koletzko et al. 2002b), and there is no known advantage of growth patterns of formula fed babies that deviate from the model of breastfed populations.

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Statement on conflicts of interest

The author declares that there is no conflict of interest, following the definitions in the guidance of the International Committee of Medical Journal Editors (http://www.icmje.org/).

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