Protein supply in infancy – a key factor for healthy growth

Scientific Summary
Introduction

Human milk is a highly complex and dynamic mixture of numerous essential ingredients. Their specific combination enables newborns to grow healthily. Compared to non-breastfed children, breastfed infants suffer fewer and shorter infections, have different growth patterns and different gut microbiota, undergo better cognitive development, and probably also have a lower risk of chronic diseases such as obesity and cardiovascular disease in later life.

We know that growth in the first years of life will exert a positive influence on long-term health and neurological development. Protein is one important factor in this growth process. The infant’s growth velocity decreases rapidly during the first months of life and afterwards slowly continues to decrease along with protein requirements for growth. Both the quantity and quality of protein in human milk change continuously over time. Trials suggest that infant formulas containing less (protein closer to the protein content in breast milk), but of the right quality, can support weight gain closer to that undergone by breastfed infants.

On the next few pages, I would like to give you a brief overview of the scientific status quo and to present a few additional expert opinions to illustrate the current discussion.
Breastfeeding – the best diet and health care measure

Mother’s own milk is the best source of nutrition for all healthy infants (Martin et al. 2016). The often used slogan “breast is best” is an oversimplification of the benefits of breastfeeding (ESPGHAN 2009). Breastfed infants experience fewer and shorter infections, have different growth patterns, different gut microbiota, better cognitive development and even probably a lower risk of chronic diseases such as obesity and cardiovascular disease in later life compared to non-breastfed children (Lönnerdal et al. 2016; Lönnerdal et Hernell 2016; WHO 2015). The promotion and protection of breastfeeding are therefore important measures for health prevention.

The CHOP (European Child Obesity Project) study, including healthy term infants from 5 European countries between 2002 and 2004 showed breastfeeding duration far from the recommendations and complementary foods introduced earlier than recommended in a sizeable number of infants (Schiess et al. 2010). In the EU, Breastfeeding experts, interest groups and mothers came together in 2004 to establish an action plan to promote breastfeeding in Europe (EU Project on Breastfeeding). According to a 2015 WHO report, Europe still has the lowest rates of breastfeeding of all the WHO regions 10 years later, although with significant differences within the European region.

The rate of early initiation of breastfeeding is very high in some European countries (WHO 2015). It is mostly the duration of exclusive breastfeeding to 6 months as recommended by the WHO and the continued breastfeeding after the introduction of solid foods that need to be improved. The information and education of expectant and new parents on the health benefits of breastfeeding for mother and child are effective measures for the promotion of breastfeeding that can be easily implemented. It is important to include mothers with lower socioeconomic status (less income, education and employment), who are less likely to begin breastfeeding.

Protein in human milk adapts to the decreasing protein requirements of the infant associated with decreasing growth velocity.

“Total nitrogen of human milk has been used for several years to calculate the protein content. (...) It became apparent in more recent years that the true protein should be calculated from the nitrogen content after subtracting the non-protein nitrogen from total nitrogen. Furthermore (...) it is likely that the amount of absorbed proteins, available for metabolism and growth is even less. These two considerations in conjunction with the recent literature on protein intake and the risk for obesity, strongly support the notion of reducing protein content of IMFs. The mechanism for optimizing protein utilization at low to moderate protein intakes and to oxidize/dispose excessive protein intakes need additional studies.”

Virgilio P. Carnielli
Professor of Neonatal-Pediatrics,
Polytechnic University of Marche, Ancona, Italy, Director of the Division of Neonatology, Azienda Ospedaliero Universitaria Ospedali Riuniti, Ancona, Italy

1: Protein requirements for growth

Adapted from Fomon et al. AJCN 1982
Non-breastfed infants also have a right to a healthy diet

Even with optimal promotion of breastfeeding, there will always be infants who depend on a substitute for breast milk because their mother cannot or chooses not to breastfeed. Along with the promotion of breastfeeding, it is therefore important to optimize the nutrition of infants needing an infant formula.

Human milk – the gold standard

The composition of the milk of healthy, well-nourished women is the model for the nutrient composition of formulas. The actual quality of an infant formula can, however, only be determined by comparing its effects on growth, plasma markers and functional outcomes (e.g. immune responses and later health) to those found in populations of healthy exclusively breast-fed infants (ESPGHAN.Koletzko et al. JPGN 2005).

Breastfed infants have different growth patterns and a lower risk of obesity in later life compared to formula-fed infants.

„The prevention of obesity is especially important, as overweight and obesity are epidemic and therapeutic interventions have shown limited success. In infancy, breastfeeding plays a central role in the prevention of overweight and obesity.“

Martin Wabitsch
Professor, Head of Division of Pediatric Endocrinology and Diabetes and of Department of Pediatrics and Adolescent Medicine, University Medical Center Ulm, Germany.
Growth and development are central characteristics of childhood. The effect of human milk on growth has recently moved into science’s focus driven by the worldwide increase of overweight and obesity, also in children. According to estimates from the WHO’s Childhood Obesity Surveillance Initiative (COSI), around 1 in 3 children in the EU aged 6-9 years old were overweight or obese in 2015. This is a worrying increase on 2008, when estimates were 1 in 4 (EU Action Plan 2014).

Research shows that breastfed children have a lower risk of obesity in later life compared to formula-fed infants (Arenz et al. 2004; Harder et al. 2005; Horta et al. 2007; Owen et al. 2005; von Kries et al. 1999; Weng et al. 2012, Patro-Golab et al. 2016). A meta-analysis based on 113 studies showed that longer periods of breastfeeding were associated with a 26% reduction in the risk (odds ratio) of overweight or obesity (Horta et al. Acta Paediatr 2015, cited by Victora et al. Lancet 2016). Among the 11 high-quality studies identified in this systematic review, the association between breastfeeding and later overweight/obesity was smaller (13% risk reduction), but remained significant.

Observational studies have shown that rapid weight gain, defined as weight gain in excess of the median by more than 0.67 standard deviations, i.e. an upward centile crossing through at least one of the major centile bands, in the first two years of life is associated with a two- to threefold increase in overweight or obesity risk in childhood, youth and adulthood (Baird et al. 2005; Monteiro et al. 2005; Ong et al., 2006). The workgroup around Koletzko et al. hypothesized that breastfeeding protects by reducing weight gain velocity during early childhood because of its different substrate supply with breastfeeding compared to feeding conventional infant formula, in particular the significantly lower protein content in human milk.

Compared with breastfeeding, feeding conventional formulas is also associated with altered body composition. A systematic review and meta-analysis of 15 studies that examined body composition in healthy infants showed that breast-fed infants had a lower fat mass at 1 year of age than formula-fed infants (Gale et al. 2012).

“With few exceptions, breastfeeding duration is shorter in high-income countries than in those that are resource-poor. Our meta-analyses indicate protection against child infections and malocclusion, increases in intelligence, and probable reductions in overweight and diabetes.”

Janusz Ksiazyk
Professor, Head of The Department of Pediatrics, Nutrition and Metabolic Diseases, Children’s Memorial Health Institute, Warsaw, Poland
Protein – the major modulator of early growth

By optimizing protein quality and reducing protein quantity in infant formula, we can achieve an approximation of early growth to that of breastfed infants. The results of a multicenter pooled analysis of individual participant data (n = 1882) from 11 randomized controlled trials (Alexander et al. 2016) shows this: The weight-for-age z-scores at 4 months of age of healthy term infants fed whey-predominant formulas with 1.8 g protein/100 kcal (lower content than in most current formulas and closer to breast milk) and improved quality from ≤ 4 weeks of age to ≥ 4 months of age were very close to the mean WHO standard (z-score 0) and the 95% confidence intervals were within ±0.5 SD (Standard Deviation) of WHO growth standards.

The effect of early protein intake on growth was tested in a large multi-country study, the European Childhood Obesity Program (CHOP) (Koletzko et al. 2009; Koletzko et al. 2014). Formula-fed infants were randomly assigned to lower or higher protein formulas (infant formula with 1.8 g and 2.2 g/100 kcal respectively, for the first 4 months and then follow-up formula with 2.9 g and 4.4 g/100 kcal respectively, until the end of the first year of life – Koletzko et al. 2009). Those in the group receiving the formulas with the higher protein content had significantly higher weight gain and, at the ages of 12 and 24 months, BMIs were significantly higher in the higher protein group, even though the intervention stopped at 12 months of age (Koletzko et al. 2009).

Follow-up to school age demonstrated lasting significant effects of early protein supply (Koletzko et al. 2014). At 6 years of age, previously breastfed infants had a significantly lower BMI than those in the control group fed higher protein formulas (Weber et al. 2014). The children fed lower protein formula in the first year of life had a BMI that was significantly lower than the control group and not different from the breastfed reference group.

“There is no doubt that early nutrition has a programming effect on an infant’s growth and development, as well as long-term health. A wealth of new evidence support the hypothesis of an association of high protein intake in early childhood and increased risk of non-communicable diseases later in life. Using low-protein formula with high protein quality in infants who are not breastfed might be one of the best ways to provide them an opportunity of developing an appropriate metabolic programming.”

Natalia Migacheva
Associate Professor, Department of Pediatrics, Deputy Director of the Institute of Professional Education, Samara State Medical University, Russia
Formulas with high protein content increase obesity risk at school age

In the CHOP-study a diet of higher protein formulas during the first year of life increased the risk of being obese at 6 years of age 2.43-fold (unadjusted) and 2.87-fold (adjusted) respectively, compared to a diet of lower protein (1.8 g in infant and 2.2 g/100 kcal in follow-up formula) formulas (Weber et al. 2014). The measurements of pre-peritoneal (PP) fat, a marker of abdominal fat, in a subgroup of children participating in the CHOP study at the age of 5 years, are also interesting. Subcutaneous fat was not different between the groups, but the PP fat layer was significantly thicker in the higher compared to the lower protein formula group (Cruszfeld et al. 2016). A thicker layer of PP fat may trigger adverse metabolic and health consequences. This observed long-term effect on later abdominal fat distribution supports the hypothesis that a high protein intake in infancy may increase the risk for cardiovascular diseases (Cruszfeld et al. 2016).

In late infancy and among toddlers, the average protein intake is 3 to 4 times as high as the physiological requirements (Fantino et al. 2008; Hilbig et al. 2006; Hörnell et al. 2013; Michaelsen et al. 2014).

Several observational studies report a positive correlation between the protein intake in later infancy and the second year of life and later obesity (Rolland-Cachera et al., 1995; Scaglioni et al. 2000). There are indications that a high dairy protein intake especially has an adverse effect on later body composition. One study, for example, shows that dairy, but not meat or cereal protein intake at 12 months is related to body fat percentages at 7 years of age (Günther et al. 2007). A current study showed that an extra 10 g of protein/day at the age of 12 months was associated with a higher BMI due to a higher fat mass index (FMI), but not with fat-free mass index, at the age of 6 years.
“Complimentary foods given to the infant can compromise the beneficial effects of breast feeding, in the Longitudinal Study of Nutrition and Growth in Children (ELANCE), breastfeeding was significantly associated with lower skinfold thickness at 20 years, when confounding variables were added to the analysis mode, as total energy and % of energy from nutrients, if such variables were not added to the model, then breastfeeding did not get any significant effect on the skinfold thickness at 20 years.”

M Sanchez Luna
MD, PhD President of the Committee of Standards of the Spanish Society of Neonatology, President of the Union of European Neonatal and Perinatal Societies, UENPS. Accredited Associate Professor of Paediatrics, Director of the Neonatology Division and NICU, Hospital General Universitario “Gregorio Marañón”, Madrid, Spain

“The first 2 years of life is probably most sensitive to high protein intake. One way to decrease protein intake is to support breastfeeding throughout at least the first year of life. If breastfeeding is not possible, infant formula composed to serve as the only food for infants should be given at least until age of 4 months.”

Hanna Lagström
Adjunct Professor, Senior Researcher, The discipline of Public Health, University of Turku, Finland. Appointed expert in the National Early Nutrition monitoring group, National Institute for Health and Welfare, Finland

(Voortman et al. 2016). The association of protein intake with FMI was stronger for the intake of animal protein (both dairy and non-dairy protein) than protein from vegetable sources. Meat may have a high protein content, but the small amounts of meat needed to ensure good iron status have a lesser impact on total protein intake (Michaelsen et al. 2014). High protein formulas and cow’s milk on the other hand can contribute significantly to excessive protein intake.

Taking into account the emerging evidence that high protein intake during the first 2 years of life is a risk factor for the subsequent development of overweight and obesity, it seems prudent to avoid a high protein intake in excess of metabolic requirements during the first 2 years of life (Michaelsen et al. 2014). This could be accomplished with a dynamic formula-stage-system in which protein content and quality reflect changes in human milk and the changing requirements of the infant.
The longitudinal evolution of protein in human milk: model for a dynamic “staging” of infant formula

Both the quantity and quality of protein in human milk change continuously over time

In the past, human milk was divided into 3 stages – colostrum, transitional milk and mature milk, which begins to appear at around two weeks after the infant’s birth (EFSA 2014). Protein quantity and quality in mature human milk, however, continue to change. The protein content consistently decreases over time (Lönnerdal et al. 2016) (fig. 4). Concentrations of both principal proteins, casein and whey, also change profoundly over the course of lactation (Lönnerdal et al. 2016). Casein is low or absent in early lactation, then increases rapidly and then decreases along with the overall protein content in human milk (EFSA 2014). The whey protein concentration begins to decrease from early lactation and continues to fall (EFSA 2014). These changes result in a whey:casein ratio of about 90:10 in the first days of lactation, about 65:35 by week two, and 50:50 in later lactation at around 6 months (EFSA 2014; Lönnerdal et al. 2016). Because the amino acid contents of whey and casein proteins differ, human milk amino acid content also changes as the infant ages (Lönnerdal et al. 2016). Results of a meta-analysis of 43 studies confirmed that the protein content depends on the stage of lactation and time since delivery (Lönnerdal et al. 2016).

New 2-stage formula system with protein closer to the evolving protein in human milk

Human milk protein is unique and cannot be copied in all of its facets and its dynamic evolution. Highly developed modern protein technology has, however, made it possible to significantly improve formula protein quality. A newly developed age-optimized 2-stage formula system uses current insights from breast milk research on the evolving protein concentration in human milk during the first 12 months of lactation and the infant’s evolving protein requirements. At the center of the new concept is the development of a new age-optimized follow-up formula with a protein content below the level set in the current EU Regulation thereby better reflecting the evolving protein content in human milk (fig. 3).

“Although modifiable lifestyle behaviors in adult life are the main risk factors, substantial evidence now suggests that factors in early life also have a major role in the development of noncommunicable diseases. For instance, breastfeeding and a slower pattern of infant weight gain have been shown to reduce the risk of obesity, cardiovascular disease and diabetes in both low-income and high-income countries.”

Atul Singhal
Professor of Paediatric Nutrition, Childhood Nutrition Research Centre, UCL Institute of Child Health (ICH), UK
This new low protein formula (1.61-1.65 g protein/100 kcal) with high protein quality for infants after 3 months of age was recently tested in two randomized clinical trials (Inostroza et al. 2014; Ziegler et al. 2015). The protein content is still well above 1.30 g/100 kcal, the protein content considered adequate for infants over 3 months of age (Dewey et al. 1996; Fomon 1991, both cited by Inostroza et al. 2014). In both studies, the randomly assigned formula was to be fed exclusively from 3 to 6 months and then with complementary foods until 12 months of age. One trial in the general US population indicates significantly lower weight between 4 and 12 months of age in infants fed the low-protein formula when compared to infants on the control formula with higher protein (2.15 g/100 kcal) formula. Weight gain in the low-protein formula group was not inferior to the WHO growth standards. Longitudinal analysis of odds ratios from 4 to 12 months of age showed a significantly lower incidence of infants with weight >85th percentile (+1 SD of the mean of the WHO Standard) in the low-protein formula group compared to the higher-protein formula group.

The other trial was conducted in Chile with infants of overweight mothers (BMI >25) (Inostroza et al. 2014). Infants born to overweight mothers are prone to show accelerated weight gain during infancy (Deierlein et al. 2011, cited by Inostroza et al. 2014) and increased risk of later overweight and obesity (Yu et al. 2013). Infants fed the low-protein (1.65 g/100 kcal) formula gained significantly less weight between 3 and 6 months of age than the higher-protein (2.7 g/100 kcal) formula group, but had weight gain similar to the breastfed reference group. Weight in the low-protein formula group remained lower than that of the higher protein formula group until 2 years of age, i.e. beyond the 1-year intervention period. BMI predicted by the longitudinal analysis was significantly lower in the lower protein formula and breastfed groups than in the higher protein formula group (fig.4). BMI did not differ significantly between the lower protein formula and breastfed groups, and, at 24 months of age, were almost identical (fig. 4).

In both trials, biomarkers of protein metabolism (insulin-like growth factor-1 and C-peptide) of the low-protein groups were closer to breastfed infants than the respective biomarkers of the high-protein groups (Haschke et al. 2016).
Breastfeeding is the best option for infant feeding. It ensures the best trajectory for growth and development, while preventing non-communicable diseases in later life (WHO 2015).

Breastfeeding should be exclusive during the first 4–6 months of life and thereafter continued in combination with complementary foods.

Supporting healthy growth close to that of breastfed infants in formula-fed infants may help reduce the gap between formula-fed and breastfed infants in terms of long-term healthy weight gain and have a positive impact on risk of obesity in later life.

Breastfeeding is considered one of the most critical behaviors for health promotion and protection. A new dynamic formula system that has a high protein quality and a protein content below the regulatory limits in the EU and the United States, i.e. closer to the protein in human milk beyond 3 months after delivery, is safe for all healthy infants and can slow down accelerated weight gain, especially in infants of overweight mothers.

Considering the negative effects of excessive protein intake, especially dairy protein, during the first 2 years of age it seems prudent to better adapt the protein in follow-up formula to the protein content in human milk which decreases as the infant’s age increases.

We also thank Prof. Picaud for his contribution during the meetings and discussions.

Jean-Charles Picaud
Professor, Chef du service de Néonatologie, Hôpital de la Croix-Rousse Lyon, France
Sign up with NNI – join today!