Protein needs early in life and long-term health[1–4]

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ABSTRACT

The objective of this review was to summarize selected health aspects of protein intake during the first 2 y of life. During this period there is a marked increase in protein intake from an intake of ∼5% of energy from protein (PE%) in an exclusively breastfed infant to ∼15 PE% when complementary foods have been introduced. At this age, mean protein intake is ∼3 times as high as the physiologic requirement, but some children receive 4–5 times their physiologic requirement. Protein from cow milk constitutes a main part of protein intake in toddlers and seems to have a specific effect on insulin-like growth factor I concentrations and growth. Meat has a high protein content, but the small amounts of meat needed to ensure good iron status have less impact on total protein intake. The difference in protein intake between breastfed and formula-fed infants is likely to play a role in the difference between breastfed and formula-fed infants. There is emerging evidence that high protein intake during the first 2 y of life is a risk factor for later development of overweight and obesity. It therefore seems prudent to avoid a high protein intake during the first 2 y of life. This could be accomplished by decreasing the upper allowable limit of the protein content of infant formulas for the first year of life and limiting the intake of cow milk in the second year of life. *Am J Clin Nutr* 2014;99(suppl):718S–22S.

INTRODUCTION

Protein intake, both quantity and quality, during the first 2 y of life has important effects on growth, neurodevelopment, and long-term health. Although there is limited evidence that healthy infants in affluent countries do not receive enough protein to cover physiologic needs, there is emerging evidence that a high protein intake during the first 2 y of life may actually have long-term negative effects on health (1). Formula-fed infants receive ∼0.5 $g \cdot kg^{-1} \cdot d^{-1}$ more protein than do breastfed infants. In addition, the source of protein in infant formulas is very different from human milk such that the amino acid content of a formula-fed infant's diet is different from that of a breastfed infant's diet. Additional changes in the protein intake occur with the introduction of complementary foods into the diet. According to the 2007 WHO/FAO/UNU recommendations for protein intake, the safe level is the mean estimate for physiologic need for protein intake plus 2 SDs. The mean safe level gradually decreases from 1.77 $g \cdot kg^{-1} \cdot d^{-1}$ at age 1 mo to 0.97 $g \cdot kg^{-1} \cdot d^{-1}$ by age 2 y (2). The objective of this review was to summarize selected aspects of the health effects of protein intake during the first 2 y of life. The term "percentage of energy as protein" (PE%)[5] will be used throughout, which

simplifies the comparisons of energy requirements, energy intakes, and energy contents of food.

CHANGING PROTEIN REQUIREMENTS

One of the characteristics of the complementary feeding period is a marked increase in protein intake that occurs particularly in an exclusively breastfed infant. Expressed as PE%, breast milk contains ∼5 PE%, whereas complementary foods contain ∼15–20 PE%, a 3–4-fold increase. There is also a decrease in the PE% needed to cover the physiologic requirements during the first 2 y of life. The PE% needed in a diet to cover physiologic needs can be calculated from the total protein requirements per kilogram of body weight and average energy requirements by using the WHO/FAO/UNU 2007 recommendations. A diet with a 5.6 PE% provides the mean protein requirement at the age of 6 mo, which is close to the PE% of breast milk. The safe intake is up to 2 SDs above the mean of 5.6 PE%, or 7.7 PE%. The PE% needed to cover physiologic needs decreases during the following years. By the age of 2.5 y, the mean PE% has decreased to 3.8 and the safe intake is up to 5.2 PE%. According to the Institute of Medicine, the acceptable macronutrient distribution range for protein for the 1- to 3-y age group is 5–20 PE%, which covers the range of PE% from breast milk to complementary foods, including whole cow milk (3).

PROTEIN CONTENT OF FOODS FOR INFANTS AND TODDLERS

There is a large variation in the protein content of foods provided for infants and toddlers. The most important and typically largest source of protein is that from infant formulas and cow milk. Typical values are 5, 7–9, and 20 PE% for breast milk,

infant formula, and whole cow milk, respectively. In cow milk with reduced fat, the PE% is very high (28 PE% in 2% milk and 39 PE% in skimmed milk), which is one of the reasons that reduced-fat milks are typically not recommended for infants and toddlers. The values for meat vary between 30 and 60 PE%, depending on the fat content of the meat, but the amount of meat eaten in this age group is typically small (10–25 g/d), so that the impact on the total intake of protein is somewhat limited. For an exclusively breastfed infant who is introduced to complementary feedings without any dairy products, there is evidence that red meat is an appropriate complementary food. It is not only a good source of heme iron but also a good source of protein that differs from the protein found in human milk or infant formula (4). In fact, without the introduction of meat, these infants may have less than the ideal protein intake. It is also likely that the protein found in meat has fewer growth-promoting properties, as has been shown in older children (5).

According to studies of dietary intake at ∼12 mo of age, the average protein intake is 3–4 g/kg body weight or 14–16 PE%. In a review by Rolland-Cachera et al (6) comparing European countries, the mean protein intake was similar, except for Italy where the mean intake reported was very high (5.1 g/kg body weight or 19.5 PE%). In a large study from the United States based on the Feeding Infants and Toddlers Study (FITS) from 2008, dietary intakes of infants and toddlers were assessed (7). In the 6- to 11-mo age group, the median intake was 9 PE% and the 90th percentile was 13 PE%. In toddlers (12–23 mo) the median intake was 15 PE% and the 90th percentile was 19 PE%. Five percent of the toddlers had an intake above the upper limit of the acceptable macronutrient distribution range, which is 20 PE%. In a small recent study from Baltimore, MD, the mean (±SD) protein content in the diet of 7- to 12-mo-old infants was 9.7 ± 2.8 PE% and 13.3 ± 3.6 PE% in the 13- to 24-mo age group (8).

Thus, in late infancy and among toddlers, the average protein intake is 3 to 4 times as high as the physiologic requirements, but with a large variation.

Not only does the amount of protein differ but the quality of protein is quite variable. Infants have a wide range of intakes of amino acids because the amino acid profiles of human milk and standard cow-milk formulas are quite different. Human milk contains ∼4 times the amount of free amino acids (FAAs) that are contained in cow-milk formula (3000 compared with 600–800 μmol/L) (9). In soy-based infant formula, the content is typically 1400 μmol/L (9). Hydrolyzed formula (extensively and partially hydrolyzed) contains even higher FAA concentrations. The impact of the varying amino acid profiles is being examined and may influence growth and satiety, which, in turn, may have long-term effects.

PROTEIN AND GROWTH

The effect of early protein intake on growth and adiposity was tested in a large multicountry study, the European Childhood Obesity Program (CHOP) study (10). Formula-fed infants were randomly assigned before 8 wk of age to formulas with 2 different protein contents. For the first 4 mo, the protein content of the formulas was 1.8 g or 2.2 g/100 kcal. At the age of 4 mo, the infants were changed to formulas with considerably higher protein content. In the low- and high-protein-intake groups the

protein contents were 2.9 and 4.4 g/100 kcal, respectively. For comparison, breast milk and whole cow milk contain ∼1.4 and 5.5 g/100 kcal, respectively. 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 mo, BMIs were significantly higher in the higher protein group, even though the intervention was stopped at 12 mo. There were no differences in linear growth between the 2 intervention groups. The growth pattern in the group receiving the formulas with the lowest protein content had a growth pattern that did not differ significantly from a breastfed control group. The growth data were supported by data on insulin-like growth factor I (IGF-I) and insulin secretion measured at the age of 6 mo (11). Values of IGF-I were considerably higher in the high-protein group compared with the lower-protein group. Interestingly, the values for IGF-I in the breastfed group were considerably lower than those in the group with the low protein intake, despite the similar growth patterns. For insulin secretion, the pattern was the same, with the highest values for the high-protein group, median values for the low-protein group, and the lowest values for the breastfed group. These data underscore the difference in hormonal response between breastfed and formula-fed infants, suggesting that more than the difference in protein intake affects the hormonal response. A Danish observational study measured IGF-I and fasting insulin in infants at 9 mo of age who were well into the complementary feeding period (12, 13). Approximately half of the infants were still partially breastfed. There was a significant dose-response relation to the intake of breast milk. For both IGF-I and fasting insulin concentrations, the higher the intake of breast milk, the lower the concentration of IGF-I and insulin.

When the CHOP study was published, it was accompanied by an editorial comment (14). The editorial stated that the data reflected the complexity of the interaction between protein intake and satiety, and more data and with greater insight into the possible mechanism were needed before embarking on any changes in infant-feeding practices. Even so there has been a recent tendency of infant formula manufacturers to reduce the protein content in infant formula, to obtain a protein intake and growth pattern closer to that of breastfed infants. The US formula act allows for a wide range of protein content for infant formula, ranging from 1.8 to 4.5 g/100 kcal (15). Codex Alimentarius and the European Union directive have a lower upper limit, with an acceptable protein range from 1.8 to 3.0 g/100 kcal (16, 17).

RENAL EFFECT OF PROTEIN

A high protein intake has effects beyond those on growth. The glomerular filtration rate is increased by a higher renal solute load. If protein intake is very high during early infancy (before 4 mo), which occurs when undiluted cow milk is given at this age, the glomerular filtration rate cannot cope with the renal solute load, which results in hypernatremic dehydration. The CHOP study showed renal enlargement by ultrasound in the higher-protein-intake group compared with the lower-protein-intake group (18). In another study, renal enlargement in formula-fed infants compared with breastfed infants was shown at 3 mo (19). At a follow-up at 18 mo of age, however, there was no difference in kidney size between the 2 groups. This suggests that increased kidney size was an adaptive and reversible process. It is possible

that continuous hyperfiltration attributable to a continuous high protein intake results in glomerulosclerosis and hypertension in healthy term infants, but this seems unlikely in infants with a normal number of nephrons (20).

OVERWEIGHT AND OBESITY

An increasing number of studies have found that a high protein intake during the first 1 to 2 y of life is associated with an increased risk of overweight and obesity later in childhood. The CHOP study found that the effect of a high protein intake for the first 12 mo of life resulted in a higher BMI at age 2 y (10). Several observational studies have reported significant positive associations between protein intake at 12–24 mo of age and BMI measured at 4 and 8 y (1, 21–25). A limitation of these studies is that the children were only followed until 8 y of age and only 2 of the studies measured body composition to show that protein intake was positively associated with body fat (23, 25).

In contrast to the effect of early protein intake on later overweight and obesity, it is interesting that the effects of fat intake during the first 2 y of life seem to have little or no effect on later obesity. In a review by Agostoni and Caroli (26) on the role of fat intake in the first 2 y of life and the later development of noncommunicable diseases, it was concluded that there was no evidence of any convincing association between fat intake during the 6- to 24-mo age period and later indexes of adiposity. That there is no association was further supported by a recent small study by Rolland-Cachera et al (27), suggesting that a higher fat intake early in life might even protect against overweight. In this study, which was a follow-up of an observational cohort, there was a significant negative association between fat intake at age 2 y and both body fat mass and serum leptin concentrations at 20 y of age. It was suggested on the basis of this and other studies that restriction of fat intake in early life may activate adaptive mechanisms to prevent underweight, thus increasing susceptibility to overweight, metabolic disease, and leptin resistance later in life.

BODY COMPOSITION AND IGF-I

During the first 2 y of life, there are marked changes in body composition. Skinfold thickness, BMI, and body fat increase up to the age of ∼9 mo, and decrease thereafter followed by another increase at ∼6 y of age. Diet also seems to have a marked effect. In a meta-analysis of 15 studies, Gale et al (28) showed that breastfed, compared with formula-fed, infants gained more fat during the first 6 mo of infancy and less fat during the second 6 mo of life. It is likely that differences and changes in protein intake over time play a role in these changes in body fat composition. In a review of recent studies on IGF-I and nutrition in early life, it was suggested that, in terms of healthy infants, there was a pattern of decreased IGF-I values until ∼9 mo of age, after which there was an increase (29). This pattern is the opposite of the pattern of change seen in BMI, which peaks at ∼9 mo of life. Because IGF-I values in early life are stimulated by protein intake, and are associated with changes in body composition, it is speculated that protein could have an important role in the development of body composition; however, more research is needed.

FAAs AND APPETITE

An emerging aspect of protein intake in early life is the effect of FAAs on appetite regulation. Mennella et al (30) found that infants randomly assigned to an infant formula with hydrolyzed cow-milk protein, which has a high content of FAAs, ingested less formula compared with those receiving a normal cow-milk–based infant formula and had a growth pattern closer to that of breastfed infants. In another study, glutamate, one of the most abundant FAAs in hydrolyzed infant formula, was added to a cow-milk whole-protein infant formula (31). The addition of glutamate resulted in significantly shorter meal times and lower energy intake. Glutamate has an important role in satiety regulation in adults. It is the most abundant FAA in breast milk, and it might also have a role in appetite regulation in breastfed infants (32). Thus, the source of protein in infant formulas may have different metabolic effects.

FUTURE RESEARCH QUESTIONS TO CONSIDER

The following questions should be considered in future research:

- How is protein intake influencing body composition?
- What are the long-term effects of different patterns of body composition?
- During which age window is high protein intake associated with later overweight and obesity?
- What are the roles of total protein and dairy protein?

To understand the mechanisms behind associations between early protein intake, growth, and later risk of disease, there is a need for longitudinal studies focusing on the complex interaction between the following:

- Breastfeeding and complementary feeding
- Weight gain, linear growth, and body composition
- Hormonal regulation of IGF-I, insulin, and appetite hormones

CONCLUSIONS

From the age of ∼6 mo, when complementary feeding is introduced, all infants in affluent countries will have a protein intake that meets their physiologic requirements, as long as diets are not extreme and infants are introduced to appropriate complementary foods. Some infants will have very high protein intakes during the complementary feeding period, especially if they have a high intake of cow milk. Emerging data suggest that a high protein intake can have negative effects, inducing a higher growth rate, which increases the risk of later overweight and obesity. There have been some thoughts to establishing an upper level for protein intake during the first years of life that would take the risk of overweight and obesity into account. Agostoni et al (33) suggested a maximum acceptable level of 14 PE% in 12- to 24-mo-old infants. The European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) Committee on Nutrition concluded in 2008 that despite concerns that a high protein intake could increase the risk of obesity, the evidence was not sufficient to suggest an upper level of protein intake at this time (34).

Intake of cow milk is an important factor in determining total protein intake in early life. Most countries recommend waiting until after the age of 12 mo to introduce cow milk because of the

negative effect on iron status and not to avoid a high protein intake. There are no clear recommendations on how much cow milk is appropriate between 12 and 24 mo of age. The American Academy of Pediatrics recommends limiting intake of whole milk to 1 quart (32 ounces or 946 mL) (35), whereas the advice in Canada has been to limit intake to 720 mL (24 oz) (36). A suggestion for an optimal daily intake of cow milk is 500 mL/ d (37). If a 12-mo-old child weighing 10 kg is drinking half a liter of whole cow milk per day, this will provide ~38% of his or her energy needs and ~1.6 g protein/kg body weight (~50% more than the physiologic need). At this time in the United States, there is a trend for using reduced-fat milks in the second year of life for infants at risk of overweight or obesity, which ironically increases the PE% of the diet (38). Therefore, considering the emerging evidence for the negative effects of a high protein intake, it seems prudent to *1*) consider lowering the upper limit of the protein content of various formulas used in the first year of life and *2*) limit the intake of cow milk, particularly reduced-fat cow milk (which has a high PE%), during the second year of life because of its high protein content.

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