

Optimal protein intake in healthy infants^{1–3}

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The daily protein requirement and optimal protein intake in healthy full-term infants and the protein-energy ratio, safety, and long-term consequences of infant milk formula have been the subject of numerous deliberations over the past 50 y. This has been due, in part, to the paucity of data and difficulties in conducting carefully controlled studies in this population. However, despite enormous progress, significant gaps in our knowledge persist. As discussed by Fomon and Garlick (1, 2), the mean or average protein requirements can be estimated either by nitrogen balance studies or by the factorial approach. Because of the large variability, possibility of error, and difficulties in performing nitrogen balance studies, this method has not been widely used. The factorial approach represents a sum of the protein required to replace the inevitable losses from the body plus that required for growth, adjusted for so-called efficiency (1). The recommended intake of protein has been adjusted as new and more precise data on the body composition of infants and children become available (3). The recommended dietary intake is calculated by increasing the average protein requirement (by 2 times the SD) and is defined as that which meets the need of 97.5% of that specific age group (1). Thus, it represents the upper end of the recommended dietary protein intake. The current recommendation for various ages has been recently published (4). These recommendations require evaluation in clinical practice.

The study by Koletzko et al (5) in the current issue of the Journal is an important contribution that addresses an important issue and raises several interesting questions. The authors have examined the effect of lower and higher protein intake (within the recommended range) during the first 12 mo (infancy) on the growth pattern of infants until 24 mo of age. Infants born at term gestation were randomly assigned to either of 2 intervention groups and compared with a control group of exclusively breastfed (for the first 3 mo) infants. Their data show that, at 6 mo, energy intake was higher in the lower-protein group, and *z* scores for weight-for-age were higher in the higher-protein group. Body mass index (BMI) and weight-for-length remained higher in the higher-protein group at all times. The *z* score for weight-for-length at 24 mo was lower in the infants fed lower protein formula and was not different from the breastfed reference group. The authors questioned whether lower protein intake might diminish the risk of overweight and obesity. These results should be examined in the context of other published data.

The protein content of infant formula currently sold in the United States for term infants is ≈ 2.1 g/100 kcal. No specific recommendation has been made for follow-up or weaning formula, although such formulas are available (6). The minimal acceptable protein requirement of term infants has not been determined because such

studies would not be acceptable in a developing infant. The average protein requirement at 0–1 mo of age has been estimated to be 1.65 g/100 kcal. In healthy male infants, Fomon et al (7) examined whether a protein-energy ratio of 1.7 g/100 kcal was adequate and safe. Adequacy was defined as the ratio that permits growth similar to that of infants fed infant formula with relatively a generous protein-energy ratio, whereas safety was determined by the serum albumin and urea concentration. In the study by Fomon et al, energy intake and gain in weight were significantly higher, whereas gain in length was similar to the formula-fed reference group. Although the mechanism of higher energy intake was unclear, the authors concluded that, because ad libitum feeding of the experimental formula resulted in increased energy intake, a protein-energy ratio of 1.7 g/100 kcal cannot be considered safe. The observation of higher energy intake by the lower-protein group in their study is similar to the observation by Koletzko et al (5), except that it was *not* associated with increase in weight gain or BMI in the latter study. Although the 2 studies are not entirely comparable, the higher energy intake of the low-protein-formula group suggests regulation in relation to satiety and energy requirements. Another study of lower protein intake did not show any significant effects (8).

The higher weight gain associated with higher protein content of formula is not surprising, considering that fat is the only accessible site to store excess carbon. Others have made similar observations. An association between weight gain during infancy, childhood, and adolescence and the development of obesity and metabolic syndrome in adults has been reported in a number of clinical epidemiologic studies. Systematic reviews of these studies have specifically examined the association between rapid weight gain during infancy and subsequent obesity (9, 10). These data have been difficult to compare because of the wide variability in study design, duration of observation and therefore weight gain exposure, definition of infant obesity or weight gain, definition of obesity at outcome, and differences in age at outcome. For these reasons, the effect size has been difficult to evaluate and the outcome difficult to predict. Nonetheless, these data show a robust association between rapid weight gain during infancy and subsequent obesity. However, quantification of “rapid” weight gain

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remains a problem. Ong and Loos (9) transformed the reported effect size to a standard infancy weight gain exposure, defined as >0.67 change in weight SD score (corresponding to the difference between displayed centile lines on standard growth charts). Their analysis showed a higher odds ratio for obesity with longer duration of infancy weight gain exposure, with younger age when the outcome was measured, and when less or no adjustment for potential confounding factors was made. These analyses provide strong evidence that rapid weight gain during the first 2 y of life is associated with obesity in later life.

On the basis of these data, should we consider prescribing low-protein formula to infants? The answer most likely is a categorical no. The present data only point to the complexity of interaction between intake and satiety, their regulation, and their effect on growth. We need much more data and greater insight into the mechanisms before embarking on any change in infant feeding practice.

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