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Protein and Energy Requirements of the Preterm/Low Birthweight (LBW) Infant

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The growth and development of the normally growing, breast-fed, term infant is universally recognized as ideal. Hence, the term infant's requirement for any nutrient can be defined as the amount present in a reasonable volume of human milk, usually the average volume ingested daily based on careful studies in groups of infants whose intakes were determined by difference in weight before and after each feeding. This is the basis of the most recent dietary reference intake of protein and most all other nutrients for the 0–6-mo-old infant (1).

Unfortunately, no such standard exists for the LBW infant. Rather, for the past 25 years, the protein and other nutrient requirements for these infants have been defined as the amounts necessary to support intrauterine rates of growth and nutrient accretion (2). Despite the many advantages of human milk for reducing infection and promoting better neurodevelopmental outcomes in both term and preterm infants (3), preterm infants fed unsupplemented human milk do not grow at the intrauterine rate (4). Further, even if the total protein, calcium, phosphorus, sodium, and even zinc contents of a reasonable volume of human milk were absorbed and completely retained, the amounts retained would not be sufficient to support the intrauterine rates of accretion (5 6). This review addresses some of the many pressing issues concerning standards of growth for the preterm infant as well as strategies for providing optimal protein intakes.

INTRAUTERINE RATES OF GROWTH AND NUTRIENT ACCRETION

A priori, the requirements to support intrauterine rates of growth and nutrient accretion should equal the amount of each nutrient transferred from the mother to the fetus. While these data are available for some animal models (7), they are not available for human infants. However, the lack of such data may not be a serious drawback. Since the metabolic and environmental milieu of the fetus and the *ex utero* preterm neonate are different, providing individual nutrients at fetal delivery rates may not be an optimal strategy for postnatal feeding. For example, there is little uptake of lipid by the fetus of any species, before mid-late gestation. Therefore, energy metabolism of the fetus is not dependent on availability of fat until late in the third trimester and, even then, dependence on fat availability is minimal. Glucose delivery to the fetus occurs at low fetal insulin concentrations and at a rate that reflects energy utilization. Amino acid uptake by the fetus, on the other hand, exceeds that needed for protein accretion and the excess is oxidized contributing significantly to fetal energy production. In contrast, lipid is a major energy source of most LBW infant feeding regimens and lipid intake usually exceeds the rate of delivery *in utero*. The LBW infant also receives glucose at higher rates than are delivered *in utero*, but almost always receives less amino acids than the fetus. These current feeding regimens promote weight gain due to body fat rather than gain in lean body mass (8). This contrast between the usual nutrient supply to the fetus (high amino acids and sufficient glucose) and what the LBW infant is fed (high intakes of lipid and glucose but low protein intake) suggests that the nutritional requirements of the LBW infant and the outcomes likely from current feeding practices be reconsidered.

Cross-sectional autopsy data concerning size and body composition of fetuses at varying gestational ages are available (9) and, from these, the requirement of most nutrients to support intrauterine rates of accretion can be estimated. The most commonly used method for estimating the protein intake necessary to maintain the intrauterine rate of protein accretion is the factorial method, which includes an estimate of inevitable urinary nitrogen losses (*i.e.*, the losses that occur in the absence of nitrogen intake) and an estimate of the amount deposited *in utero* corrected for efficiency of absorption and deposition (10).

INTAKES REQUIRED TO SUPPORT INTRAUTERINE RATES OF GROWTH AND NUTRIENT ACCRETION

An alternative method is to determine the actual intakes that support intrauterine rates of growth and nitrogen accretion (11). Interestingly, the two approaches do not result in the same estimate of protein requirement. The factorial method, depending upon the assumptions made concerning inevitable nitrogen losses and efficiency of absorption and deposition usually yields an estimate of ∼ 4g/kg/d to support intrauterine rates of growth and protein accretion (10). The alternative method, on the other hand, shows that a protein intake of ∼3g/kg/d supports intrauterine rates of growth and nitrogen accretion (4,11,12).

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Replicating the body composition of the fetus of the same postconceptional age as the preterm infant undoubtedly is a more desirable nutritional goal than simply achieving the fetal rate of weight gain. However, few data are available concerning body composition of infants fed different nutritional regimens. Further, considering the marked variation in clinical practice, attaining a targeted rate of weight gain in very preterm infants can be accomplished by a number of very different nutritional strategies but without consideration for "quality" of weight gain. Since nutritional regimens that produce excessive fat deposition could put the infant at risk for long-term adverse health outcomes, regimens that result in excessive fat deposition are suspect. *A priori*, replicating intrauterine body composition changes postnatally seems to be a more physiologic approach to growth in the very preterm infant. Currently, measuring actual body compositions of very preterm infants is difficult.

If the requirements for supporting intrauterine rates of growth and nutrient deposition are introduced at birth, the infant, in theory, should continue to deposit nutrients and increase in size as if birth had not intervened. However, few, if any, LBW infants can successfully make the transition to the necessary enteral intake until days to weeks after birth. Thus, at discharge, often several weeks after birth, most infants weigh ~2 SD less than the fetus of comparable postconceptional age (13,14). Initially, most infants lose from 10% to 20% of initial weight. Some of this, perhaps about half, is excess extracellular fluid and probably is of little consequence to the infant, but the remainder represents either failure to accrete lean mass and/or fat at a reasonable rate or actual loss of lean mass and/or fat. Loss of lean mass may have adverse consequences, but the consequences of loss of fat mass or failure to deposit fat are not clear.

Most infants do not regain birth weight before at least 2 wk of age and many of the smallest infants do not do so until much later (13,14). Thus, even if intakes sufficient to support intrauterine rates of nutrient accretion are provided throughout the remainder of hospitalization, the infant will remain behind the fetus of the same postconceptional age for some time. The consequences of this growth delay or "postnatal growth restriction" are not known with certainty, but there is concern that it contributes to the smaller size and lower developmental indices of former LBW infants that have been documented as late as early adulthood (15). This is certainly true for severe malnutrition during infancy and early childhood and timely treatment of such infants has been shown to improve both long term growth and developmental outcome (16). Many LBW infants, however, also have a variety of clinical problems that may contribute to their less than optimal growth and neurodevelopmental outcome (14). Nonetheless, assignment of preterm infants to be fed a nutrient-enriched *versus* a standard formula for only ~4 wk before hospital discharge has been shown to result in substantial neurodevelopmental advantages at 18 mo of age as well as at 7.5 y and ~15 y of age (17–19).

Despite some uncertainty about the long term consequences of inadequate nutrient intake and growth restriction during early extra uterine life, until recently it has seemed reasonable to at least attempt to overcome early postnatal growth failure. Strategies that have been advocated include more optimal parenteral nutrition early in the infant's neonatal course and earlier introduction of adequate enteral intake (20).

PREVENTING EARLY LOSSES OF BODY PROTEIN STORES

Several studies have shown that the early loss of body protein stores daily can be minimized or prevented by providing as little as 1–1.5 g/kg/d of amino acids parentally even if concomitant energy intake is as low as 30 kcal/kg/d (11,21–27). This modest intake, however, will not promote growth and, as a result, deficits will continue to increase. Thus, higher parenteral amino acid intakes which appear to be well tolerated (21–23), even with a modest concomitant energy intake, have been advocated. In one of the more recent such studies (21), a higher parenteral amino acid intake for only 24 h produced increases in protein deposition of ELBW/VLBW preterm infants. This prospective, randomized study included 28 infants (mean weight ~950 g) who received an amino acid intake of either 1 $g \cdot kg^{-1} \cdot d^{-1}$ or 3 $g \cdot kg^{-1} \cdot d^{-1}$ beginning at an average postnatal age of ~24 h. Metabolic studies showed that protein balance, measured by both nitrogen balance and leucine stable isotope methodologies, was significantly higher with the higher amino acid intake. Moreover, there was no evidence of toxicity with the higher amino acid intake; there were no statistically significant differences between groups in the amount of sodium bicarbonate administered, the degree of metabolic acidosis as determined by base deficit, or the BUN concentration. Plasma concentrations of essential and nonessential amino acids (except threonine and lysine) in the 3 $g \cdot kg^{-1} \cdot d^{-1}$ group, were similar to those of normally growing 2nd and 3rd trimester human fetuses who were sampled by cordocentesis (28) whereas, in the 1 $g \cdot kg^{-1} \cdot d^{-1}$ group, concentrations of most amino acids were at least 50% lower than fetal concentrations. Such data support the concept that more aggressive early parenteral nutrition may significantly mitigate the early postnatal growth failure of most preterm neonates.

"CATCH-UP GROWTH"

The amino acid and energy intakes necessary to support intrauterine rates of weight gain and protein accretion, whether administered parenterally or enterally, are ~3 g/kg/d and ~90 kcal/kg/d (29). However, these intakes will not abolish any loss of lean body mass that occurred before the infant's regaining birth weight. Doing so requires an additional allowance for "catch-up" growth and this allowance varies considerably from infant to infant. For example, the infant who does not regain birth weight until 28 d of age has twice the "catch-up" needs of an infant who weighs the same at birth but regains birth weight at 14 rather than 28 d of age. In both cases, the needs for "catch-up" growth are additional to the needs for supporting intrauterine rates of growth and protein accretion. These differing needs for "catch-up" growth make it difficult to define a single protein requirement that is appropriate for all preterm LBW infants; rather, each infant is likely to have a unique requirement consisting of the need for maintaining intrauterine rates of growth and protein retention (~3.0 g/kg/d) plus the needs for "catch-up" (see below).

Kashyap *et al.,* using data obtained in more than 200 infants fed protein and energy intakes ranging from 2.25–4.3 g/kg/d and 100–150 kcal/kg/d, respectively, have developed multiple regression equations for predicting protein and energy intakes needed to produce different rates and composition of weight gain and have shown that the predicted intakes achieve the desired rates and composition of weight gain (30). Using these equations, Heird (20) has predicted the protein and energy intakes necessary to result in different rates of "catch-up" growth for a theoretical infant who weighs 690 g at birth and is discharged weighing 1830 g. Had this theoretical 690 g infant remained *in utero* and deposited protein and fat at intrauterine rates, weight would have reached 1830 g in 56 d. The protein and energy intakes required to support this rate and composition of weight gain is ~3.0 g/kg/d and 90 kcal/kg/d, respectively, the amounts shown to support intrauterine rates of growth and protein accretion (4,11,12,29). However, an infant who is born weighing 690 g and does not regain birth weight until 14 d of age must increase from 690 to 1830 g in 42 d to weigh the same and have the same body composition as a fetus of comparable postconceptional age. The predicted protein and energy required to support this rate of growth are 4 g/kg/d and 109 kcal/kg/d. If the same infant does not regain birth weight until 21 d, weight must reach 1830 g in 35 d to "catch up" to the fetus of comparable postconceptional age. In theory, this will require protein and energy intakes of 4.9 g/kg/d and 123 kcal/kg/d from 21 d until discharge (weighing 1830 g). While many infants receive the theoretical energy intakes recent experience with the theoretical protein intake required is limited.

Although the protein requirement for LBW infants varies considerably depending largely on how long it takes to regain birth weight and the amount of "catch-up" growth desired, this concept is difficult to apply to feeding individual infants. For the latter, an intake that meets the needs of most infants is needed. Currently, modern preterm formulas and supplemented human milk provide protein intakes of 3.3 to 3.6 g/kg/d and an energy intake of 120 kcal/kg/d. These intakes, once established, support growth and protein accretion rates somewhat in excess of intrauterine rates (11) but, as noted above, most infants fed these intakes remain below the tenth percentile of modern intrauterine standards at discharge (13). Hence, with respect to growth, it is clear that most preterm/LBW infants are likely to benefit from a higher protein intake. However, there is no clear evidence that an energy intake of more than 120 kcal/kg/d is desirable. A higher energy intake may promote somewhat better protein utilization but it also is likely to result in higher rates of fat accretion, the desirability of which is questionable. Unfortunately, data concerning body composition of infants fed different protein and energy intakes are not available.

More optimal early nutrition, both parenteral and enteral, obviously will reduce the time required to regain birth weight (11,20) and, hence, reduce the protein needed to support "catch-up" growth. Nonetheless, most infants are likely to require a higher protein intake from supplemented human milk and formula than is currently provided. Thus, recent recommendations reflect this likely need for a higher protein content of human milk fortifiers and preterm formulas. A Committee appointed by the Life Sciences Research Organization to evaluate the nutrient contents of preterm infant formulas (31) recommended a maximum protein content of 3.6 g/100 kcal (4.3 g/kg/d at an energy intake of 120 kcal/kg/d) rather than the usual maximum of ~3.0 g/100 kcal (3.6 g/kg/d at an energy intake of 120 kcal/kg/d).

BENEFICIAL UNDERNUTRITION

Although a higher protein intake undoubtedly will improve growth and possibly reduce neurodevelopmental deficits (17–19), recent data suggest that rapid early growth may result in unfavorable markers of cardiovascular risk (*e.g.*, lipid profile, blood pressure, leptin resistance and insulin resistance (32)) at 13–16 y of age. Some of these unfavorable effects appear to be related to feeding formula *versus* human milk (33,34). However, all effects were associated with higher *versus* lower rates of growth in early infancy. These adverse effects on markers of cardiovascular risk were substantial; if they persist beyond 13–16 y of age, as seems likely, they have major public health implications. These potentially advantageous effects of slower growth during infancy on markers of cardiovascular risk must, of course, be balanced against the demonstrated adverse effects of relative undernutrition during infancy, particularly the adverse effects on neurodevelopmental outcome, which also have important public health implications as well as implications for the quality of life of the affected individuals and their families.

The concept of "beneficial under-nutrition" has a broad biologic basis. The phenomenon of improved life expectancy following long periods of low growth rate from relative undernutrition has been demonstrated in *Drosophila*, rats, and possibly humans who undergo prolonged periods of low caloric intake. In contrast, catch-up growth (*i.e.*, accelerated growth rates) at the "wrong time" in development shortens life span, promotes obesity, and impairs glucose tolerance in the rat, decreases body fat in the Atlantic salmon, and decreases resistance to starvation in the speckled wood butterfly (35). In humans, rapid rates of growth in childhood reportedly increases the risk for cardiovascular disease, hypertension, obesity, and type 2 diabetes later in life, but slower growth appears to be protective against later development of cardiovascular disease (36). Thus, while beneficial in the short term, "catch-up" growth may be harmful in the long term (37).

THE NEONATOLOGIST'S DILEMMA

Resolution of the dilemma between potentially favorable effects of slower rates of growth and, hence, lower nutrient intakes during infancy on future cardiovascular health *versus* demonstrated adverse effects of poor growth on neurodevelopmental outcome (17–19) will require long term prospective studies of hundreds to thousands of infants or a novel retrospective study of perhaps even more infants. The latter, of course, can be accomplished sooner. However, such studies are not possible unless reliable data concerning early intakes and rates of growth are available. Without such data, retrospective studies, of course, will be much more difficult to interpret and also less reliable.

The importance of resolving this dilemma cannot be overestimated. Doing so is one of the greatest challenges to neonatal nutrition today. Further, it must be resolved before progress can be made toward better defining the nutrient needs of preterm/LBW infants, particularly their protein and energy needs. Ongoing studies will soon provide data concerning the association between early growth and cardiovascular risk factors beyond 13–16 y of age; if the same or more substantial adverse effects on markers of cardiovascular risk are observed at this later age, it is likely that prospective studies focusing on the relationship between protein intake and rates of growth during infancy and markers of cardiovascular risk as early as 7–7.5 y of age may suffice. In resolving this dilemma, it is important to distinguish between effects of early rates of growth *versus* the composition of early growth. It also is important to reconcile the association between rapid early growth and later adverse effects on cardiovascular health with earlier findings linking small size at birth as well as small size at a year of age to similar adverse effects in adults (38,39).

Until this dilemma is resolved, the neonatologist is left with a number of unanswered questions regarding postnatal nutrition of the very preterm infant. Some of these include the following: Is the early neonatal period a "vulnerable" time for preterm infants in terms of postnatal metabolic programming? If so, is this vulnerability related to gestational age or to postnatal age? If "accelerated growth" at "the wrong time" has adverse long-term effects, when and in which infants is catch-up growth advisable? Is the postnatal growth failure seen in very preterm neonates an example of "beneficial undernutrition?" What is the balance between providing sufficient protein and other nutrients to assure optimal developmental outcome but avoid undesirable metabolic programming? Is early aggressive nutrition, which has been emphasized repeatedly for the past decade and is finally being accepted by neonatologists, beneficial or detrimental?

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