Regulation of proteolysis and optimal protein accretion in extremely premature newborns

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ABSTRACT
Growth outcomes for extremely premature infants remain poor, and improving growth in this population will require a better understanding of how to limit proteolysis and promote protein accretion. Extremely premature infants exhibit high rates of proteolysis that are unrestrained by physiologic increases in insulin, intravenous amino acids, and full parenteral nutrition. Imbalances in current amino acid solutions may be in part responsible for the inability of parenteral nutrition to reduce proteolysis in preterm infants. However, amino acids in parenteral nutrition are effective for increasing protein synthesis in extremely preterm infants, which leads to improved protein balance. Current evidence suggests that early administration of 3 g amino acids · kg⁻¹ · d⁻¹ to extremely premature infants is safe and effective. Enteral nutrition may be more effective than parenteral nutrition in limiting proteolysis and producing protein accretion in preterm infants, but the protein content of current preterm formulas may be inadequate for supporting optimal growth in this population. Important areas of future research include determining whether altered intravenous amino acid solutions can better effect reductions in proteolysis, investigating the effect of enteral nutrition on proteolysis and protein accretion, and conducting a large randomized controlled trial of formula with a higher protein content. Am J Clin Nutr 2007;85(suppl):621S–4S.

KEY WORDS Premature infants, proteolysis, protein accretion, growth, stable isotope tracers, leucine, phenylalanine

INTRODUCTION
Growth outcomes for extremely low-birth-weight (ELBW) infants (those weighing <1000 g at birth) remain poor. Information collected by the National Institutes of Health Neonatal Network has documented that 90–99% of ELBW infants have weights that are less than the 10th percentile at 36 wk corrected gestational age (1, 2). Other large groups have also reported poor growth outcomes for ELBW infants (3). Improving growth in ELBW infants will require a better understanding of how to limit proteolysis and achieve better protein accretion in this population.

PROTEOLYSIS IN PREMATURE AND TERM NEONATES
High rates of proteolysis are a characteristic of immature individuals, and rates of proteolysis in ELBW infants are >2-fold those measured in healthy adults (3, 4). A reduction in the overall rate of proteolysis in response to nutrient intake is an important mechanism whereby protein is preserved in adults; however, suppressing proteolysis in ELBW infants appears to be more difficult. For example, intravenous glucose infusion resulting in an increase in insulin concentrations reduces proteolysis in adults (5), but ELBW infants respond differently. Hertz et al (6) assessed proteolysis in ELBW infants by measuring the rates of appearance of the essential amino acids phenylalanine and leucine at 2 different glucose infusion rates. An increase in the glucose infusion rate from 6 to 9 mg · kg⁻¹ · min⁻¹ produced a 3-fold increase in insulin concentrations, but overall rates of proteolysis (as reflected by the leucine and phenylalanine rates of appearance) were unchanged (Figure 1).

Amino acids are potentially important regulators of proteolysis, and the ability of intravenous amino acids to suppress proteolysis has been evaluated in full-term infants. In healthy term infants, graded infusions of intravenous amino acid produce a dose-dependent suppression of proteolysis (Figure 2, 7). At an amino acid intake of 1.2 g · kg⁻¹ · d⁻¹, proteolysis is reduced by ≈10%. In response to a doubling of amino acid intake to 2.4 g · kg⁻¹ · d⁻¹, proteolysis is reduced by ≈20%. These reductions in proteolysis occur without changes in glucose and insulin concentrations. Premature neonates, on the other hand, demonstrate resistance to changes in proteolysis in response to intravenous amino acids. Clinically stable premature (=32 wk gestation) infants have been studied in the first week of life with the use of a protocol identical to that used in the term infant study described above (8). In contrast with the case in their term counterparts, rates of proteolysis are unchanged in response to the graded infusion of intravenous amino acids. The differences between the 2 populations are illustrated in Figure 2.

Even when amino acids are provided along with lipid and glucose in quantities sufficient to support growth, overall rates of proteolysis in extremely premature (26 wk gestation) and premature (32 wk gestation) infants are little affected. Illustrated in Figure 3 is the percentage change in proteolysis in response to parenteral nutrition containing 90 kcal · kg⁻¹ · d⁻¹ and amino
acid intake of 2.5 g · kg⁻¹ · d⁻¹ in 26 wk gestation infants, 32 wk gestation infants, and term infants all studied during the first week of life (9, 10). Full parenteral nutrition reduces proteolysis by 17% in full-term infants, but has minimal effect in preterm infants.

Insulin is a powerful regulator of proteolysis in adults (4), but as discussed previously, physiologic increases in insulin do not appear to affect proteolysis in ELBW infants. To determine the effect of pharmacologic levels of insulin on whole-body proteolysis in ELBW infants, Poindexter et al (11) used the glucose clamp technique. Although high concentrations of insulin (80 μU/mL) effectively reduced proteolysis in these infants by 20%, protein synthesis was diminished by a similar magnitude, which resulted in no change in overall protein balance. Unexpectedly, lactate concentrations tripled during the insulin infusion and acidosis was observed. At present, it is difficult to support insulin infusions as part of nutritional therapy to reduce proteolysis and improve protein accretion on either efficacy or safety grounds.

COMPOSITION OF AMINO ACID SOLUTIONS AND PROTEOLYSIS

It remains unclear why intravenous nutrition has a limited ability to reduce overall rates of proteolysis in premature infants. One potential explanation is that amino acid solutions do not contain all amino acids. Glutamine, cysteine, and tyrosine are absent from current neonatal amino acid solutions. Note that cysteine can be added to the solution just before its administration, and tyrosine is provided as N-acetyl-tyrosine in some amino acid products. However, because of limited bioavailability, N-acetyl-tyrosine appears to be a poor source of tyrosine (12).

Kalhan et al (13) evaluated the effect of supplemental glutamine on overall proteolysis in preterm infants, and showed a significant reduction in whole-body rates of proteolysis when glutamine was added to parenteral nutrition. However, there was no net change in overall protein balance, and a large multicenter trial of glutamine supplementation in parenteral nutrition in ELBW infants showed no effect on growth (14). Some preliminary data suggest that the addition of cysteine may reduce proteolysis and improve protein accretion in extremely preterm infants (15), and other studies have suggested that cysteine may increase protein synthesis in premature infants (16, 17). Because tyrosine may be a limiting amino acid in current solutions (10), examining the effect of a more bioavailable form of tyrosine (glycyl tyrosine) on overall proteolysis and protein accretion in preterm infants is an important area of future research.

EARLY INTRAVENOUS AMINO ACID USE AND PROTEIN ACCRETION

Whatever the limitations of current amino acid solutions in inhibiting proteolysis in extremely premature infants, it is clear that early amino acid use results in significant increases in protein synthesis and improved protein balance, even at low caloric intakes. Rivera et al (16) reported protein synthesis rates to be ≈40% higher in preterm infants who received amino acids at 1.5 g · kg⁻¹ · d⁻¹ than in those who received glucose alone; leucine and protein balance were also significantly improved (Figure 4). As in previous studies, no significant difference in overall proteolysis rates was observed between the 2 groups. Thureen et al (18) examined the effect of 1 versus 3 g amino acids · kg⁻¹ · d⁻¹ on protein kinetics and balance in extremely preterm infants within the first few days of life. Protein synthesis rates were ≈35% higher (and rates of proteolysis unchanged) in the group who received the higher amino acid intake (Figure 4). Preterm infants receiving 3 g amino acids · kg⁻¹ · d⁻¹ also had significantly more positive protein and leucine balances (18). Other studies in preterm infants have produced similar results (9, 17), and no adverse metabolic consequences (as evidenced by amino acid concentrations, blood urea nitrogen concentrations, ammonia concentrations, or acidosis) have been observed with early amino acid administration (9, 16–18). There appears to be a
lower rates of proteolysis and improved protein accretion compared with parenteral nutrition alone.

ENTERAL PROTEIN INTAKE AND OPTIMAL PROTEIN ACCRETION

Even when extremely preterm infants transition from parenteral nutrition to full enteral nutrition, optimal protein accretion remains a significant clinical challenge. Embleton et al (22) reported accumulating protein deficits in preterm infants aged <30 wk receiving full enteral intake with standard preterm formulas, which suggests that there may be a benefit in increasing the protein content in enteral formulations. Zello et al (23) showed that there is a linear correlation between protein balance and protein intake in preterm infants consuming a fixed caloric intake; these studies were conducted at protein intakes ranging from 1 to 3.6 g·kg⁻¹·d⁻¹. Recently, Cooke et al (24) reported a significant positive relation between protein intake and protein balance at higher protein intakes (3.4—6.2 g·kg⁻¹·d⁻¹). In that crossover study, preterm infants were randomly assigned to receive standard preterm protein content formulas (3 g per 100 kcal) or high protein content formulas (3.6 g per 100 kcal). Weight gain and protein accretion were significantly greater when the infants received the high protein content formula (Figure 6). Given the poor growth outcomes experienced by most extremely preterm infants, a large multicenter randomized controlled trial examining the effect of a higher protein content formula in this population is important and necessary.

FIGURE 6. Mean (±SE) protein intake and balance and weight gain in premature infants receiving regular-protein preterm formula (3.0 g per 100 kcal; □) or high-protein preterm formula (3.6 g per 100 kcal; ■). *Significantly different from regular-protein formula, P < 0.005. Data are from reference 24.

ENTERAL NUTRITION AND PROTEOLYSIS

Enteral nutrition in premature infants may be more effective than parenteral nutrition in reducing proteolysis and promoting parenteral protein accretion. The splanchnic organs exhibit high rates of proteolysis, and parenteral nutrition may have limited ability to reduce proteolysis in these organs (20). van der Schoor et al (21) measured lysine kinetics in preterm infants in a period of full enteral feeding as well as during a period of combined parenteral (60%) and enteral (40%) feeding. Protein and lysine intakes were similar in the 2 periods. Rates of proteolysis were substantially lower (≈40%) during full enteral nutrition, although because of small numbers of subjects (n = 4), the change was not significant (21). Overall protein balance (as reflected by the essential amino acid lysine) was significantly greater during full enteral nutrition (Figure 5). Further detailed study of the effect of enteral nutrition on proteolysis and protein balance in premature infants is clearly warranted. Because many extremely preterm infants do not achieve full enteral feeds for weeks, it will be useful to examine whether combined parenteral and enteral nutrition can result in linear relation between amino acid intake and accretion (18), and beginning amino acid infusions to extremely preterm infants at 3 g·kg⁻¹·d⁻¹ is effective in preserving protein stores and achieving at least modest protein accretion. In addition to the data showing the short-term efficacy and safety of the provision of early amino acids to preterm infants, recent information also supports the longer term safety and efficacy of such an approach, at least through early infancy (19). Despite this evidence, early administration of sufficient quantities of amino acids to preterm infants is far from a universal practice in neonatal intensive care units (19).
In summary, early delivery of intravenous amino acids at 3 g · kg⁻¹ · d⁻¹ can significantly improve protein accretion and growth outcomes in extremely preterm infants, and available data support both short-term safety for metabolic indexes and longer-term safety through early infancy (9, 16, 17, 19). Although additional information about long-term outcomes is desirable, the current evidence suggests that the clinical practice of delivering sufficient quantities of early amino acids to extremely preterm infants should be more widely adopted. Preterm infants appear to be resistant to the anti-proteolytic effect of parenteral nutrition, and studies examining whether altering amino acid composition (in particular, examining a more bioavailable form of tyrosine) to better affect reductions in proteolysis are warranted. In addition, a further systematic investigation of the effect of full enteral nutrition and combined enteral and parenteral nutrition on proteolysis and protein accretion is important. Finally, the protein content of current preterm formulas appears to be inadequate for extremely preterm infants, and a large, well-designed study evaluating the effect in this population of a formula with a higher protein content is of high priority.

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REFERENCES


