Optimizing Early Protein Intake for Long-Term Health of Preterm Infants

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Abstract

The idea that early protein intake may influence, or program, long-term health in preterm infants is strongly supported by decades of research starting from the early 1980s. At this time, it was recognized that preterm infants required a high protein intake to achieve postnatal growth closer to the intrauterine growth rate of a normal fetus of the same post-conceptional age, a goal regarded optimal for short- and long-term health. Subsequently, follow-up of preterm infants randomized to different neonatal diets demonstrated that those receiving higher protein intakes that promoted growth had benefits for brain structure and function up to 16 years later, but also detrimental effects on cardiovascular risk factors such as insulin resistance and adiposity. These effects of early growth on risk of metabolic disease, termed the ‘growth acceleration’ hypothesis, have been demonstrated in randomized and observational studies in infants born preterm and at term. Nevertheless, on balance, current nutrition policy for preterm infants is based on the consensus that supporting optimal neurodevelopment is the neonatologist’s highest priority. Therefore, this policy appropriately favors early administration of a high protein intake to benefit neurodevelopment, irrespective of any increase in cardiovascular risk. The current review will consider the evidence underlying this policy.

Introduction

Preterm birth is a global public health issue and a leading cause of death in children under 5 years [1]. Both the incidence and survival from preterm birth have been increasing, which means that more adults have a history of prematurity.
According to the WHO, the incidence of premature birth has increased in 62/65 countries in the last 20 years [1], while survival has increased in many countries [2] (e.g. in the US survival of infants <28 weeks of gestation has increased from 72 to 76% from 2004 to 2011). However, survival is not enough and much of what we do on the neonatal intensive care unit is to improve long-term outcomes, particularly for neurocognitive development. Consequently, the focus of nutrition for preterm infants has changed from meeting nutritional requirements to the impact of early nutrition on long-term health.

The idea that nutrition in early life may influence, or program, later health has a 50-year history in animal biology [3], but has only recently been applied to humans. This concept is particularly relevant to infants born prematurely. In fact, the first experimental (randomized) evidence that early nutrition can affect later health was obtained in infants born preterm [4]. In the early 1980s, it was recognized that preterm infants required a high protein intake in order to achieve a postnatal growth rate closer to the intrauterine rate of growth of a normal fetus of the same gestational age. This high protein intake was subsequently shown to improve later cognitive development [4]. However, more recent evidence suggests that faster neonatal weight gain also increases risk factors for cardiovascular diseases such as obesity and insulin resistance [5].

The current review, therefore, aims to consider the impact of early nutrition on later health of infants born preterm, focusing on the risk/benefit of accelerated growth secondary to a high protein intake. The review will highlight the substantial limitations in our knowledge and emphasize the need for further research into optimal nutrition for the preterm infant, a problem which affects 1 in 10 newborns (approximately 15 million births) worldwide per year [1].

**Underlying Concepts for Feeding the Premature Infant**

In 1985, the American Academy of Pediatrics defined optimal nutrition of the premature infant as that required to mimic the intrauterine growth rate of a fetus of the same postconceptional age [6]. However, this basic concept does not account for the huge differences in physiology between a fetus and an ex utero premature infant; it does not consider large changes in body composition (a fetus in utero gains more lean tissue than a preterm infant ex utero), and, most importantly, the concept is not based on evidence of effects of nutrition on health outcomes. Consequently, it has been argued that the optimal nutrition of preterm infants should be that which allows the infant to achieve optimal short- and long-term health.
Although this concept provides a basic framework for nutritional goals for the preterm infant, it remains unclear whether growth rates matching the intrauterine rate can be achieved, or indeed are desirable, for long-term health. Nevertheless, postnatal growth retardation is almost universal in infants of very low birth weight born prematurely, and hence the importance of meeting the higher nutritional requirements of preterm compared to term infants is widely accepted, particularly for protein intake [7]. As a result, in order to reduce postnatal undernutrition and growth faltering, recommendations for protein intake in preterm infants have increased progressively over the last 20 years (currently: 3.5–4.0 g/kg per day for infants weighing between 1–1.8 kg and 4.0–4.5 g/kg per day for infants <1 kg) [8]. Furthermore, to prevent a catabolic state in the first few days after birth, there has been increased emphasis on early introduction of amino acids, the so-called ‘aggressive’ nutritional approach [9]. However, while these increases in protein intake are likely to be beneficial for short-term health, the evidence that early protein intake can improve long-term outcomes remains limited and is largely based on observational data rather than randomized trials that are required to establish a causal link between early nutrition and long-term neurodevelopment.

**Protein Intake and Later Neurocognitive Development**

The most widely cited study to support the impact of increasing protein intake on later health of infants born prematurely was the large randomized controlled trial conducted by Lucas et al. [4] in the early 1980s. In this study, 926 infants (birth weight <1,850 g) were randomly assigned to the standard diets available at the time (term formula containing 1.5 g/100 ml protein or donated breast milk with approximately 1.0 g/100 ml protein) or to a nutrient-enriched preterm formula (containing 2.0 g/100 ml protein together with some extra energy, calcium and phosphate) [4]. The diets were given as a supplement to the mother’s own milk or as a sole diet to infants of a mother who chose not to provide breast milk. Follow-up at 7.5–8 years of age showed 12.2 points higher verbal IQ in boys given the enriched formula, and, in both sexes combined, more infants fed term formula (31%) had low verbal IQ (i.e. <85) than those given preterm formula (14%; p = 0.02). Subsequent follow-up of a subset of this cohort (that included only infants born <30 weeks of gestation) showed that the effects of early nutrition on verbal IQ persisted at 16 years of age [10]. Importantly, adolescents in the high nutrient group had practical benefits for cognitive function (e.g. mathematical reasoning, numerical operations and reading comprehension) [Isaacs, unpubl. data]. Infants receiving the protein-enriched formula (for an average of
only 4 weeks) also had approximately 10% larger volumes of the caudate nucleus (which was related to verbal IQ in males), thereby supporting the hypothesis that a higher early protein intake had permanent beneficial effects on the structure of the brain [11].

Although strongly supporting the impact of a higher protein diet on later cognitive development, this trial has several limitations. For example, the effects of nutrition were seen only for verbal IQ (and not performance IQ) and only in males. Only a small subset of the cohort was followed to 16 years of age, raising the possibility of selection bias [10]. Moreover, there were no differences in IQ between infants randomized to preterm formula versus those receiving donor human milk despite large differences in protein intake between groups. Despite its low protein content, donor breast milk appeared to be protective against neurocognitive impairment possibly because of an unknown protective factor or higher quality of protein in human milk. Finally, it was not certain that the benefits for cognitive function were related to a higher protein intake alone rather than more energy, or a greater supply of some essential component, such as calcium or phosphate or a particular amino acid.

Nonetheless, the concept that postnatal growth retardation in the preterm infant is associated with impaired later neurodevelopment is supported by numerous observational studies [12, 13]. Poor growth in head circumference appears to be particularly important and strongly associated with impaired later cognitive function [13, 14]. Randomized trials have shown that poor head growth can be ameliorated by increasing early protein intake [15], although the effects of the increase in head growth on long-term neurodevelopment are less clear.

As opposed to the impact on growth, relatively few studies have investigated the direct effects of neonatal nutritional intake on later neurocognitive development. In a retrospective analysis, Stephens et al. [16] showed that each gram of protein taken per kilogram per day in the first week was associated with an 8.2-point increase in the Mental Development Index at 18 months of age, strongly supporting a link between early protein intake and later neurodevelopment.

However, despite extensive observational data, the concept that a high protein intake in infants born preterm improves long-term neurodevelopment remains unproven. There are strong associations between early protein intake and neonatal growth, and between neonatal growth and later neurodevelopment, but there is limited evidence for a direct causal link between early nutrition and later cognitive function. Recent studies, which are based on higher protein intakes than historical reports in which protein intakes of some infants were very low [4, 16], do not support an association between higher protein intake and later neurodevelopment. For instance, in a comparison of cohorts before and after changes in nutritional policy in the neonatal intensive care unit to increase protein
intake, although a higher protein intake (from 3.3 to 3.8 g/kg/day) was associated with better growth there was no effect on neurodevelopment at age 2 years [17]. Furthermore, a Cochrane systematic review concluded that, although early administration of amino acids (within the first 24 h compared to after 24 h) is associated with a positive nitrogen balance, there was a lack of evidence for benefits for late growth or neurodevelopment [9]. Unexpectedly, in one study, early and high intravenous amino acid administration was associated with a lower Mental Development Index at age 18 months [18]. Finally, a recent Cochrane systematic review found that, although higher protein intake (≥3 but <4 g/kg per day) in formula-fed low-birth-weight preterm infants accelerated weight gain, there was lack of data to support benefits of higher protein for later neurodevelopment [19]. Clearly, therefore, there is need for a trial powered to detect the impact of early protein intake on later neurodevelopment rather than growth. One such trial (ProVIDe: ACTRN12612001084875), which aims to investigate the effect of increasing protein intake (by 1–2 g/kg per day in the first 5 postnatal days) on survival free from neurodevelopment disability at age 2 years, is currently recruiting and could help define optimal protein intake for infants born prematurely.

**Protein Intake and Later Growth and Bone Health**

In contrast to effects on neurodevelopment, there is little evidence to support a role for higher protein intake on long-term growth or bone health of infants born preterm. Adult stature of most survivors of prematurity is within the expected range although they are on average shorter [20]. However, despite huge differences in neonatal protein intake, follow-up of the Lucas trials from the 1980s [4] found no effects of early nutrition on stature at age 7–8 years [21] or 20 years [22]. Similarly, although young adults born preterm have lower bone mineral density [23], neonatal protein and calcium or phosphate intake did not affect peak bone mass [22]. Interestingly, a higher proportion of human milk consumption in the neonatal intensive care unit was associated with greater whole-body bone mass at age 20 years possibly as a consequence of nonnutritive beneficial factors in human milk [22].

**Protein Intake and Later Risk Factors for Cardiovascular Disease**

Follow-up of the same preterm nutritional trials from the 1980s suggested that faster postnatal weight gain, as a consequence of higher protein intake, increased later risk factors for cardiovascular disease. Unexpectedly, infants randomized
to protein-enriched preterm formula compared to the standard diet had a greater risk of obesity, dyslipidemia, blood pressure and insulin resistance 13–16 years later [5]. Faster neonatal weight and length gain was also associated with endothelial dysfunction, an early stage in the atherosclerosis process [24]. However, even in preterm infants with the highest weight gain, endothelial function did not differ from healthy term infants suggesting that low weight gain in preterm infants was beneficial rather than an appropriate weight gain having a detrimental effect [24]. This observation suggests that, since most preterm infants had early postnatal growth faltering (downward centile crossing), promotion of faster growth in these infants to prevent growth faltering was unlikely to increase their risk of metabolic diseases to levels higher than those seen in healthy infants born at term.

The counterintuitive idea that a high rate of neonatal growth could have detrimental effects on long-term health led to the ‘Unifying Postnatal Growth Acceleration Hypothesis’ [5]. This hypothesis proposed that faster postnatal growth (upward centile crossing) could explain the cardiovascular benefits of breastfeeding (since breastfed infants have slower growth than those given formula) and the detrimental effects of being born small for gestational age (since these infants show rapid catch-up growth after birth) [5]. Subsequently, the growth acceleration concept has been confirmed in >50 observational studies collated in several systematic reviews [summarized in ref. 25], including in infants born preterm [5, 24–28], and in randomized trials in term infants born both appropriate and small for gestational age [25]. The evidence is consistent across studies and includes an individual-level meta-analysis in 47,661 participants from 10 cohorts [reviewed in ref. 25]. Overall, these studies suggest a large effect size. For example, in healthy term infants, over 20% of the later obesity risk can be explained by the rate of infant weight gain, and the relative risk of later obesity associated with more rapid weight gain in infancy ranges from 1.2 to as high as 5.7 [25].

Importantly, the association between rapid weight gain between birth and term-corrected age and the long-term tendency to risk factors for cardiovascular disease persists in young adults born preterm [28]. In a follow-up of a Dutch cohort of adults born prematurely (mean age of 21 years), those with the highest quartile for gain in weight relative to length from birth to term had a significantly higher body fat percentage, waist circumference, acute insulin response and disposition index in early adulthood than the subgroups with moderate and low gain in weight for length. Therefore, as is common in biological systems, faster weight gain in infants born preterm appears to have both a short-term benefit and long-term costs [25]. The mechanisms for these long-term effects of early growth are poorly understood but include possible epigenetic changes and
programing of hormonal systems that affect appetite regulation [reviewed in ref. 25]. Optimal nutrition in the preterm infant, therefore, has to take into account both the long-term benefits (for neurodevelopment) and adverse effects (for cardiovascular disease) of promoting weight gain in the neonatal period.

**Overview**

Based on the above discussion, it appears that optimal protein intake in the preterm infant for long-term health probably depends more on the outcome of interest rather than a concept such as mimicking the rate of weight gain of a fetus in utero. Faster neonatal weight gain may favor better neurodevelopment, while slower weight gain may decrease risk factors for cardiovascular disease. Nevertheless, on balance of risks, the current nutritional policy for preterm infants is based on the widely accepted consensus that supporting optimal neurodevelopment is the neonatologist’s highest priority. The strength of the evidence from observation studies, randomized trials showing benefits of a high protein intake for head growth and follow-up of the preterm nutritional trials from the 1980s argue for a nutritional strategy that provides a high protein intake to prevent postnatal growth faltering. Importantly, lifestyle interventions in later life may be able to modify cardiovascular risk factors in adults born prematurely, but it is very unlikely that any interventions will correct deficits in cognitive development. Therefore, the risk-benefit ratio clearly favors early and high administration of protein in order to improve later cognitive function, irrespective of any increase in the cardiovascular risk.

However, this consensus is largely based on research that has focused on infants <31 weeks of gestation [4, 10] and it is uncertain whether the risk-benefit ratio of faster weight gain differs for the larger, more mature, healthy preterm infant versus those with extreme prematurity. Accelerated weight gain is a risk factor for long-term obesity and cardiovascular disease in term infants born small for gestational age, and the current nutrition policy does not encourage promotion of catch-up growth in these infants [29]. Therefore, the gestational age at which low-birth-weight preterm infants should be fed like a term infant and given a standard protein intake to reduce later risk of metabolic disease rather than a higher protein intake to improve neurodevelopment is not known (but unlikely to be a strict cut off at 37 weeks or lower). Furthermore, the amount of protein within the current recommended range that has optimal benefits for long-term health at different gestational ages requires further investigation. Finally, the critical window for programming effects of early growth and nutrition is unknown, and whether the same nutritional policy should
apply after discharge from the neonatal intensive care unit is controversial. Few studies have investigated the effects of growth in the first year after birth on later cognitive function, although in one such study, each additional z-score gain in weight between term and 12 months corrected age was associated with a modest neurodevelopmental advantage at age 8 years (1.9 points higher on the Wechsler Intelligence Scale for children) but only small adverse effects on blood pressure (a systolic blood pressure increase of 0.7 mm Hg) [30]. Clearly, further research is needed to address these questions. Ultimately, as pointed out by Kerkhof et al. [28], the aim must be to define the optimal target of postnatal weight gain and protein intake after preterm birth with regard to neurodevelopment as well as health in adulthood.

Disclosure Statement

The author declares that no financial or other conflict of interest exists in relation to the contents of the chapter.

References

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