Dietary proteins and IGF I levels in preterm infants: determinants of growth, body composition, and neurodevelopment

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It has been demonstrated that a high-protein diet in preterm born infants during the first weeks of life may enable a growth rate equal to that seen *in utero* and may also result in a better long-term neurodevelopmental outcome. This diet may limit immediate postnatal growth retardation and may hence lower the risk of increased fat deposition after birth leading to the metabolic syndrome in later life. Insulin-like growth factor I (IGF I) has proven to play an important role in early postnatal growth of preterm infants, but also seems to have a persisting influence on body composition in childhood. Furthermore, increased IGF I concentrations in preterm infants have been associated with improved neurodevelopmental outcome. This review will elaborate on the role of dietary proteins and IGF I on growth, body composition, and neurodevelopment of preterm infants. Possible causal pathways will be explored and areas for future research will be proposed.

Postnatal growth restriction is a major problem faced in the care for preterm infants. At 36 wk postmenstrual age, 91% of all preterm infants show postnatal growth restriction (weight ≤1.3 SD) (1). At term age, ~30% of infants are reported to still be growth restricted (2). As survival rates of preterm infants with an increasingly younger gestational age rise, we are subsequently confronted with the long-term sequelae of preterm birth. At 11 y of age, 40% of children born before 26 wk of gestation have been reported to have serious neurocognitive impairment and moderate to severe impairment of neuromotor function, vision and hearing was reported in respectively 10, 9, and 2% of cases (3). Preterm birth and postnatal growth restriction have both been associated with impaired neurodevelopmental outcome (4). However, Franz *et al.* found that only a small percentage of the variability, roughly 3%, of the mental processing composite score was explained by growth (5). There might be a common factor leading to both poor growth and poor neurodevelopment, e.g., a poor nutritional status or major neonatal morbidities. Nonetheless, several studies suggest that there might be independent pathways (5,6). Either way, these poor outcomes warrant an intervention. Furthermore, preterm infants are prone to develop risk factors for the onset of the metabolic syndrome. They are reported to have lower insulin sensitivity, increased blood pressure and increased fat mass in childhood and young adulthood (7–9). Nutritional interventions in these infants have been found to influence the development of risk factors for the metabolic syndrome (10). Hence, neonatologists are challenged to compose and administer a diet which limits postnatal growth restriction; yet with caution to also limit the development of risk factors for the onset of the metabolic syndrome.

Dietary factors, endocrine function, and the simple immaturity of organ systems are entangled in the endeavor to optimize postnatal growth and metabolic programming. Dietary proteins are essential in enabling a growth rate similar to intrauterine growth (11). Nevertheless, the balance between proteins and other nutrients are essential to understand how growth and body composition in preterm infants can be optimized. Insulin-like growth factors (IGF) are a key in the endocrine regulation of growth. Notably, IGF I has an anabolic and mitogenic effect which is crucial for symmetric growth due to the presence of the IGF I receptor in multiple cell types and tissues. Moreover, IGF I synthesis in multiple peripheral tissues causes it to function as an auto- and paracrine factor which does not merely influence growth, but also organ functioning. IGF I's possible influence on neurodevelopmental outcome may be potentiated through its trophic effect or through altering the functioning of the central nervous system.

In this review, we aim to explore the possible pathways relating neonatal dietary protein intake and IGF I levels to growth, body composition, and neurodevelopmental outcome in infancy, childhood, and young adulthood.

IGF I REGULATION

IGF I is a small polypeptide which is mainly synthesized in the liver. It stimulates cell division, cell growth, cell motility, glucose uptake, and protein synthesis. Furthermore, IGF I inhibits apoptosis. Prenatally it is secreted into the blood under control of insulin. Postnatally growth hormone (GH) gradually takes over this role. In addition, malnutrition and

hypothyroidism negatively influence IGF I plasma levels. IGF I is also synthesized in multiple peripheral tissues, e.g., kidney, bone, and muscle, where it is released under control of GH and local factors. 99% of IGF I in plasma is bound to high affinity IGF binding proteins which control IGF I transportation and distribution (12).

THE ROLE OF IGF I IN GROWTH AND BODY COMPOSITION
Fetal IGF I levels gradually increase during pregnancy to reach ~46–90 ng/ml at term age (13). After preterm birth, IGF I levels slowly increase (14). Meanwhile, infants born at term show a quick surge in IGF-I levels (15). **Figure 1** illustrates postnatal IGF I levels in preterm and term infants.

In preterm infants, IGF I levels at birth are positively correlated with birth weight (16). Until term age, these infants IGF I levels' are also positively correlated with their preceding as

well as their subsequent weight gain, indicating higher previous as well as higher subsequent growth rate in those infants with higher IGF I levels (14).

However, after term age contradictory findings have been reported. Several studies observed IGF I levels to positively correlate with current growth parameters and preceding growth velocity in preterm as well as healthy term infants (17–20). In contrast, findings concerning the correlation between IGF I levels and subsequent growth velocity are inconclusive (**Table 1**). Hypothesizing these findings might reflect that after term age a turning point occurs. At this point, infants with the lowest IGF I levels and thus the poorest previous growth may tend to show accelerated growth. This hypothesis would be in line with the negative correlation between IGF I and subsequent growth velocity found in the above stated studies: infants with the lowest IGF I levels had the highest subsequent
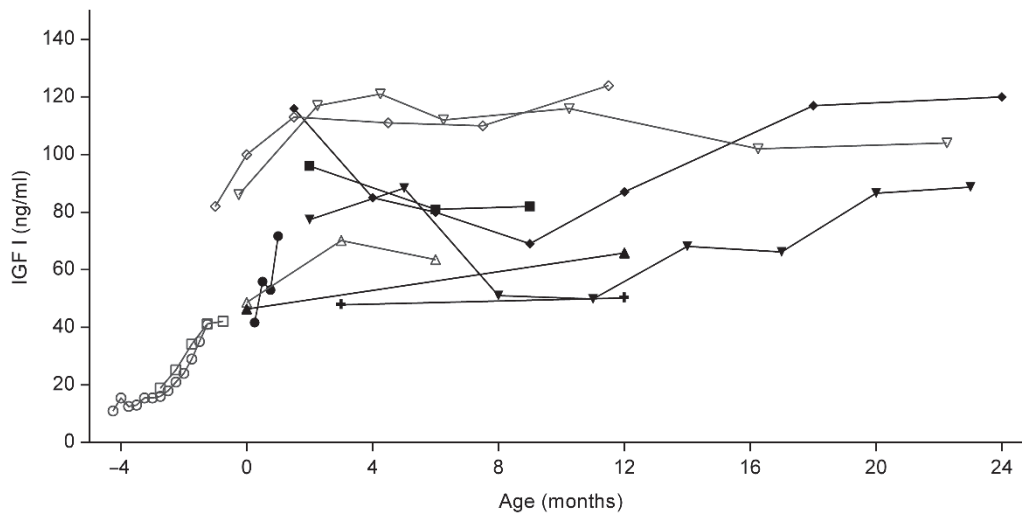

Figure 1 Postnatal insulin-like growth factor I (IGF I) levels in preterm and term infants. Preterm infants: Hansen-Pupp (open circle) (14), Ohkawa (open square) (80), van de Lagemaat (open triangle) (18), Giapros (open diamond) (20), Wang (open, inverted triangle) (81). Term infants: Iniguez (closed triangle) (82), Kurtoglu (closed circle) (15), Wang (closed diamond) (81), Larnkjaer (closed square) (37), Hyun (closed, inverted triangle) (83), and Ong (plus) (28).

Table 1 Associations between IGF I and growth

	van de Lagemaat (18)	van de Lagemaat (18)	Giapros (20)	Chellakooty (17)	Ong (28)	Socha (19)
Study population	Very preterm infants	Very preterm infants	Late preterm infants	Healthy term infants	Healthy term infants	Healthy term infants
Timing IGF I blood draw	Term age	3 mo	6 wk, 3 and 6 mo[a]	3 mo	3 mo	6 mo
IGF I and previous growth velocity	↑ Δ weight SDS (birth to term age)	↑ Δ weight SDS (birth to 3 mo[b])	↑ weight[c]	↑ Δ weight SDS (birth to 3 mo)	Not reported	↑ Δ WFL SDS (birth to 6 mo)
	↑ Δ length SDS (birth to term age)	↑ Δ length SDS (birth to 3 mo[b])	↑ length[c]	↑ Δ length SDS (birth to 3 mo)		
IGF I and current growth	↑ weight and length SDS	↑ weight and length SDS	↑ weight and length SDS	↑ weight; → length	↑ weight; →length	↑WFL SDS
IGF I and subsequent growth velocity	↓ Δ weight SDS (term age to 6 mo[b])	→ Δ weight SDS (3–6 mo[b])	→ (growth parameters not specified)	↓ Δ weight SDS (3–18 mo)	→ Δ weight (3–12 mo)	→ Δ WFL SDS (6–12 mo)
	↓ Δ length SDS (term age to 6 mo[b])	→ Δ length SDS (3–6 mo[b])		→ Δ length SDS (3–18 mo)	↑ Δ length (3–12 mo)	

IGF I, insulin-like growth factor I; SDS, standard deviation score; WFL, weight-for-length. ↑ = positive correlation; ↓ = negative correlation; → = no correlation; Δ = gain.
[a]Chronological age. [b]Corrected age. [c]Higher IGF I levels in infants with accelerated previous weight and length gain (a difference of more than 0.67 SDS between two study points).

growth velocity. Less comorbidity in preterm infants after term age might create a less stressful environment in which catch-up growth could occur, i.e., an increased growth rate compared to the infant's previous growth rate, enabling the infant to reach a body size comparable to that of healthy infants at a corresponding age. Also, further maturation of the neuroendocrine axes and target organs may improve feedback mechanisms and thus optimize growth control. Hypothesizing more into detail, eventually a point may be reached where growth velocity is fixed regardless of the previous growth pattern. This would then correspond with the absence of a correlation between IGF I levels and subsequent growth. At this point, the neuroendocrine axes and target organs may be completely programmed setting the growth rate at a fixed point.

Concluding these diverse associations may possibly illustrate a regulatory effect to direct growth towards the mean. For IGF I to function optimally, i.e., to enable growth to the full potential of each individual, certain conditions are paramount. The neuroendocrine axes and target organs need to be matured to such an extent that feedback mechanisms can reliably control growth, i.e., correct too slow as well as too fast growth. Furthermore, the environment needs to reinforce a steady growth rate; meaning that sufficient nourishment needs to be available and stressful factors, such as comorbidities, should be limited. Hypothesizing after term age there may be an optimal combination of these conditions, creating a window of opportunity to catch up in growth. In comparison, in children who are adopted from impoverished and stressful situations, growth restriction occurs. When they are placed in a more nurturing environment through adoption catch-up growth is observed. In a study by Miller *et al.*, adopted children with the lowest IGF I had 4.9 times higher odds (95% CI: 1.1–22.9) of showing catch-up growth in height than children with the highest IGF I (mean age at adoption 20.1 mo ± 9.8) (21).

Simplified, preterm infants show three growth patterns: small size at birth and persistent small size at term age (small for gestational age infants), appropriate size at birth but small size at term age (appropriate for gestational age infants with postnatal growth restriction) and appropriate size at birth and appropriate size at term age (appropriate for gestational age infants without postnatal growth restriction). In analogy with children following adoption, it is hypothesized that infants small at term age come into a less stressful period after term age which enables them to catch up in growth. Indeed *some* infants, but not all, show "catch-up" growth. The majority of this "catch-up" growth occurs in the first 6–12 mo of life (22). However there is a concern that rapid growth leads to an unfavorable metabolic and cardiovascular outcome in later life. Indeed, De Jong *et al.* found increased length gain between 6 and 12 mo corrected age and weight gain between term and 2 y corrected age to be associated with increased systolic blood pressure at 2 y corrected age (23). In addition, Singhal *et al.* found a poorer endothelial function in preterm born adolescents with the highest rate of weight gain in the first 2 wk after birth (24). In comparison, in term born young adults, rapid weight gain in the first 3 mo of life has also been associated

with decreased insulin sensitivity, a higher percentage of body fat and more central adiposity (25). Moreover, Hovi *et al.* demonstrated that a decrease in weight z-score from birth to term was associated with a higher blood pressure in adulthood. However, this association did not remain significant after adjusting for gestational age at birth (26). Nonetheless, a recent review by Lapillonne and Griffin on the effect of postnatal growth on metabolic and cardiovascular outcomes in preterm born adults concluded that, in contrast to growth during late infancy and childhood, growth up to 1 y was not associated with adult blood pressure, glucose tolerance or lipid profile (27). However, the studies described in the review were heterogenic and did not all take a possible confounding effect of nutrition and small vs. appropriate for gestational age into account. Therefore, the concern of a possible negative impact of initial growth restriction and subsequent catch-up growth expressed through several studies cannot yet be disregarded. Currently, there is no full understanding of which infants will and which ones will not completely "catch-up." As in children following adoption, one might hypothesize that infants with the lowest IGF I level in the early post term period are the ones who will show catch-up growth. However, to our knowledge as of yet, there is no evidence supporting this hypothesis in preterm infants. This hypothesis regarding catch-up growth might depend on the plasticity of the neuroendocrine axes and target organs. In certain infants, intrauterine or early-life insults may completely program the neuroendocrine axes and target organs. However, if there is some plasticity left, alteration of the growth rate may occur. This might further depend on environmental factors, e.g., lack of comorbidities and sufficient nourishment, in combination with the genetic make-up of the infant.

Remarkably, in term infants several studies did not find a correlation between IGF I and subsequent weight gain, while they did find a positive correlation with subsequent length gain. Thus, higher IGF I levels were associated with a subsequent lower BMI (28,29). This might imply that high IGF I levels protect against adiposity. Growth-restricted and preterm infants would then be at increased risk of developing obesity, because of their presumably low IGF I levels. Indeed, in small for gestational age very low birth weight infants IGF I levels up to 3 mo corrected age have been positively associated with lean mass at 2 y (30). Moreover, preterms were found to have increased fat mass and decreased lean mass in childhood (9). However, a recent meta-analysis could not confirm that this trend persists into adulthood (31).

Yet it remains to be clarified whether IGF I is primarily associated with change in height or is equally related to change in weight. Surely, IGF I is involved in bone accretion, but it is also implied in adipogenesis (32,33). Indeed Stigson *et al.* found that higher IGF I levels at a postmenstrual age of 30–32 wk were associated with increased bone mass (9). Also, a trend of higher IGF I levels was found in preterm infants who increased in bone strength compared to preterm infants with a decrease in bone strength measured by bone speed of sound (34). In line with these findings, preterm infants born small for

gestational age had decreased bone accretion at 6 mo corrected age. In addition, 20 y olds who were born preterm, especially those small for gestational age, had decreased bone mineral density and were shorter compared to term controls (35,36). Interestingly, however, others found normal bone mass in 4-y-old children who were born preterm (9). As stated by Stigson *et al.*, osteoblasts as well as adipocytes are derived from the same progenitor cells and the IGF system could be important in directing the differentiation to either adipocytes or osteoblasts (9). It may well be that states with low IGF I levels, such as critical illness, nutrient restriction and extreme prematurity, stimulate differentiation towards adipogenesis as a mechanism to ensure an easily accessible energy store, in this relatively catabolic state, as compared to anabolic states with high IGF I levels where sustainable growth through bone formation might be obtained.

Nevertheless, the role of IGF I in growth, body composition, and development of the metabolic syndrome remains complex. For instance, lower IGF I levels in infancy have been associated with higher IGF I levels in later life (37). This suggests that events in early life can program IGF I and possibly metabolic outcomes in later life. However, low as well as high IGF I levels in adulthood have been associated with the metabolic syndrome and cardiovascular disease (38). Therefore, it is difficult to give a clear-cut view of the role of IGF I alone in growth, body composition, and the development of the metabolic syndrome.

THE ROLE OF IGF I IN NEURODEVELOPMENT

In clinical studies, brain and cranial growth have been associated with subsequent neurodevelopment (5,39). A polymorphism in the IGF I promotor gene, which is known to regulate serum IGF I levels, has been related with slower cranial growth from birth until 5 y of age (40). Moreover, Hansen-Pupp *et al.* found IGF I levels to correlate with brain volumes while there was no association with cerebral spinal fluid volume. The authors hypothesize that this could imply that IGF I does not limit atrophy secondary to brain damage, but rather stimulates brain growth (41). In premature infants, a higher rate of increase of IGF I until 35 wk postmenstrual age has directly been related to a better neurodevelopmental outcome at 2 y of age (39). In line with that, Okuma *et al.* found that IGF I levels were associated with white matter organization (42). Interestingly, mean IGF I concentration was positively correlated to neurodevelopmental outcome during a period, from 30 to 35 wk postmenstrual age, when a surge in IGF I levels occurred and infants started growing after a phase of postnatal growth restriction (14,39). This may suggest that IGF I has to reach a certain level before it can enhance neurodevelopmental outcome. Even so, the premature disruption of the maternal-placental-fetal unit alters more neuroendocrine factors than merely IGF I, which also influences the final neurodevelopmental outcome.

In analogy with the development of retinopathy of prematurity, the sudden decrease in IGF I at birth could cause stagnation in vascular growth. It is hypothesized that the surge in IGF I might lead to neovascularization with abnormal vessel formation, which could cause intracranial hemorrhage and consequently influence neurodevelopmental outcome. In experimental studies it has been suggested that IGF I may limit damage after hypoxic-ischemic brain injury and inflammation (43,44). Moreover, mice treated with IGF I seemed to have increased proliferation of immature oligodendrocytes, while the number of mature oligodendrocytes remained the same. This was hypothesized to possibly promote myelination at later stages when the immature oligodendrocytes mature and start myelinating (45). In addition, lipopolysaccharide induced brain inflammation in a mouse model led to lower IGF I levels and impaired myelination in the subcortical white matter (46). However, in a rat periventricular leukomalacia model, it was demonstrated that exogenous IGF I limited lipopolysaccharide induced damage at a low dose, while it increased damage at higher doses (47). Recently, IGF I administration has been investigated in a phase I study in preterm infants and showed to effectively increase IGF I levels without any adverse events (48). In the near future, this might offer a therapeutic intervention potentially improving neurodevelopment as well as growth and body composition.

THE ROLE OF DIETARY PROTEINS IN GROWTH AND BODY COMPOSITION

In the first weeks of life preterm infants, almost universally accumulate a protein deficit and show postnatal growth restriction. In an attempt to achieve an intrauterine-like growth rate, neonatologists are challenged to administer the right composition of amino acids and the optimal amount of proteins, combined with sufficient fatty acids and carbohydrates, to optimize nitrogen accretion. Currently, the recommended range of protein intake for preterm infants is 3.5–4.5 g/kg/d (49). Over the past few years, increasing amounts of parenteral amino acids have been administered to preterm infants showing a consistent increase in protein balance. Recent nutritional studies have actually demonstrated that by administering high dose parenteral amino acids current recommendations for protein intake and intrauterine-like growth rates can be achieved, nutritional deficits can drastically be reduced and postnatal growth restriction can in part be prevented (**Figure 2**) (11). It is recognized that high and early introduction of proteins can limit the initial postnatal weight loss (50). By reducing initial weight loss, the tendency for rapid "catch-up" growth might be reduced, which may lead to more favorable metabolic programming. Indeed, low protein levels are associated with low IGF I levels (51), which in turn is associated with fat mass accretion in childhood (30).

However, after the initial period of weight loss, in which parenteral feeding is the primary source of nutrition, growth sets in. When growth occurs, protein requirements can be re-evaluated and slowly tapered off to reach 2–3 g/kg/d at term age (52). Caution is warranted to maintain an appropriate protein intake when transitioning from parenteral to enteral nutrition. However, enteral and parenteral protein intake might not be similar. For instance, bypassing the enteral route is likely to
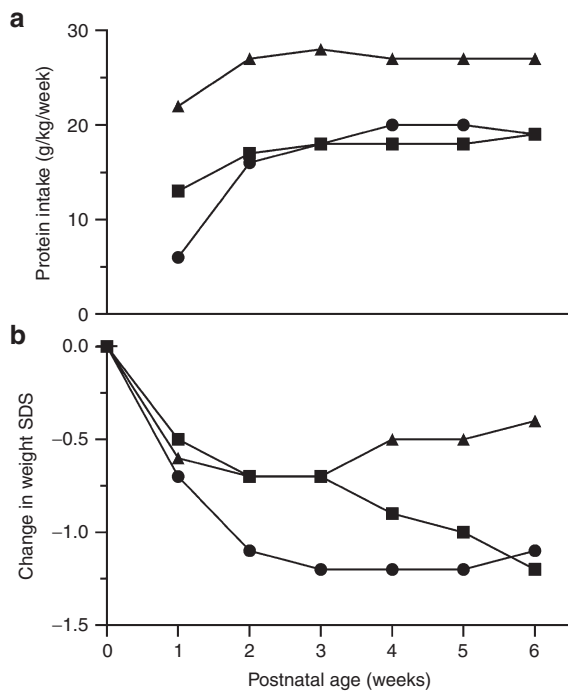
Figure 2 Protein intake and change in weight z-sore. (**a**) Protein intake and (**b**) change in weight z-score in the first 6 wk of life achieved by standard practice in our neonatal intensive care unit in Amsterdam, The Netherlands (square) (M. Krikke, unpublished data) compared with that reported by Embleton (circle) (84) before current ESPGHAN guidelines and Senterre (triangle) (85) using current ESPGHAN guidelines.

lower the systemic availability of certain amino acids which are metabolized from other amino acids in the intestine and/or liver (50).

In spite of several studies which did not find an increased growth after augmenting protein intake (53,54), most studies demonstrate that increased protein intake in the neonatal period positively influences growth up to term age (55–59). These studies report improved absolute and standardized measures of weight, length and head circumference as well as an increased growth velocity. No intolerance of high-protein diets has been reported (52,60) and glycaemic control might actually be improved with a high protein intake (53,54). However, protein intake in the neonatal period will not necessarily have an impact on growth indices in childhood (59). A high protein intake in the in-hospital as well as in the post discharge period seems to decrease fat mass and increase lean mass up to 6 mo corrected age (61–63). Whether this trend persists into childhood is not known. Using bone transmission time, Scattolin *et al.* found protein intake to positively correlate with bone mineral status at 36 wk postmenstrual age (60). However, Fewtrell was unable to correlate protein intake in infancy with peak bone mass or bone turnover in young adulthood (36). Thus, a persisting beneficial effect of early protein intake on growth and body composition in later life has not yet been confirmed.

Even though protein is vital to optimize growth, its relation to other nutrient components and the administration of specific amino acids are equally important. Indeed, Mcleod *et al.* demonstrated that an increased protein/energy ratio reduced

adipose tissue accretion as compared to muscle accretion. Surely, energy from another source than protein itself is necessary for net protein gain. However, when non-protein caloric intake surpasses 60 kcal/kg/d, protein intake itself is the primary determinant of protein gain. Nevertheless, it should be questioned to which level the protein/energy ratio should be increased. The ESPGHAN committee on nutrition recommends a ratio of 3.2 to 4.1 g protein/100 kcal (49). Yet there is a need of supportive evidence as to which ratio should be maintained at specific points in time. Several studies found that when preterm infants were on complete enteral nutrition increasing the protein/energy ratio above 3 g protein/100 kcal did not improve fat free mass accretion compared to a ratio of 2.7–2.8 g protein/100 kcal (61,64). To our knowledge studies conducted so far have not assessed the effects on body composition of various protein/energy ratios in the first 2 wk of life. Because preterm infants have limited ability to synthesize certain non-essential amino acids those amino acids become conditionally essential. Some have proposed that the addition of these so called semi-essential amino acids to the diet of preterm infants will improve growth. Cysteine for example, has been implied to be one of the key factors which potentiate the trophic effect of high-protein diets (65).

THE ROLE OF DIETARY PROTEINS IN NEURODEVELOPMENT

During hospitalization increased protein intake improves head growth in preterm infants (66,67). Even so total energy and lipid intake also have been positively correlated with head growth (67,68). Nonetheless, Hansen-Pupp *et al.* could not associate protein and caloric intake with brain volumes (39) and in several studies protein-enriched nutrition failed to improve neurodevelopmental outcome up to 18 mo corrected age (53,66,69,70). Macro- and microstructural brain analyses could not be correlated to intake of protein or other nutritional components either (42). Yet, two studies by Stephens *et al.* and Cormack *et al.* showed that protein intake in the first weeks of life was positively correlated with the cognitive and motor score on the Bayley Scales of Infant Development (71,72). In addition, Biasini *et al.* found that increased protein intake in extremely low birth weight infants improved performance and hearing/language scores on the Griffith Development Mental Score at 3 and 12 mo corrected age (73). Moreover, increased fat free mass, which is claimed to reflect protein accretion, was associated with faster neuronal processing at 4 mo corrected age (74). Also, perinatal protein restriction in mice altered the intracerebral dopamine circuit which caused altered reward-processing and hyperactivity (75). The authors suggest that this could possibly be translated to adverse neurodevelopmental outcome, such as ADHD, in growth-restricted infants. Furthermore, in preterm infants who were fed a high-nutrient diet larger caudate volumes and higher verbal IQ were found in adolescence (76).

So far, pathways explaining the association between neurodevelopment and protein intake are still speculative. Compared to other nutrient components the unique feature of protein might just lie in the alteration of neuronal processing. Perhaps

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that the underlying mechanism works through increased neurotransmitter- and receptor synthesis. Indeed, increased lactalbumin intake in rats increased cortex tryptophan. Nevertheless, casein had a negative effect on tryptophan (77). Also, de Kieviet *et al.* found an increased oral glutamine intake to be associated with increased volumes of white matter, hippocampus, and brain stem in very preterm children at school age (78). Since glutamine has been shown to reduce the number of serious infections in very preterm children, they hypothesized that increased glutamine intake indirectly influences neurodevelopment by reducing infections in the neonatal period.

IGF I AND DIETARY PROTEINS

As stated earlier, IGF I levels are related to nutritional intake. Socha *et al.* demonstrated that infants fed high-protein follow-up formula had higher IGF I levels than those fed low-protein follow-up formula (19). Moreover, a minimal caloric as well as a minimal protein intake has to be reached to maintain normal IGF I levels (12). Furthermore, there is a strong negative effect of breast milk on IGF I levels. Next to the lower protein content other, yet to be determined, factors might play a role in establishing this effect (79). Given the reciprocal relation between IGF I and nutrition, nutritional interventions might be the key factor in improving growth, body composition and neurodevelopmental outcome of preterm infants. Interestingly, Hansen-Pupp *et al.* found that IGF I and nutritional intake only correlated after a postmenstrual age of 30 wk (14). The timing of a nutritional intervention may therefore be crucial for the sustainability of its effect.

CONCLUSIONS

Altogether, preterm and small for gestational age infants are at risk for impaired growth and a suboptimal body composition, making them prone to risk factors for the metabolic syndrome. Low early postnatal IGF I levels seem to be at the origin of this problem. Increased early dietary protein intake has shown to improve growth and body composition in infancy. However, it is yet to be elucidated whether this trend persists in later life, thus calling for long-term follow-up studies.

Higher IGF I levels and increased dietary protein intake have been found to also improve neurodevelopmental outcome of preterm infants. Evidence supports a trophic role of IGF I in the development of the central nervous system. So far, signs of a direct mechanism which limits damage from hypoxic-ischemic and inflammatory insults have only been found in experimental studies. However, it is plausible that improved neuronal processing due to higher IGF I levels and an increased dietary protein intake may play a role in preterm infants.

Since IGF I levels are related to dietary protein intake it would be valuable to investigate whether a nutritional intervention could improve the long-term outcome of preterm infants by optimizing IGF I levels as well as optimally using the potential of IGF I. It may be argued whether initial IGF I levels are sufficient or should be further increased by increasing nutrient intake in the early postnatal period. On the other hand, nutrient intake might have to be reduced once IGF I reaches the level where it's trophic and neurodevelopment enhancing potential becomes effective, creating a more favorable setting for further development. Moreover, assessment of the optimal protein/energy ratio in this period may be a key to improve metabolic programming and studies on specific amino acids could ameliorate dietary advices. In addition, it has to be questioned whether IGF I administration to preterm infants could offer a potential future therapeutic intervention. Altogether, the above illustrates the important gap of knowledge in potential causal pathways between dietary protein intake, IGF I levels and long-term outcomes of preterm infants that needs to be explored in future research.

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