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Early Influences of Nutrition on Postnatal Growth

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Abstract

Health and nutrition modulate postnatal growth. The availability of amino acids and energy, and insulin and insulin-like growth factor-I (IGF-I) regulates early growth through the mTOR pathway. Amino acids and glucose also stimulate the secretion of IGF-I and insulin. Postnatal growth induces lasting, programming effects on later body size and adiposity in animals and in human observational studies. Rapid weight gain in infancy and the first 2 years was shown to predict increased obesity risk in childhood and adulthood. Breastfeeding leads to lesser high weight gain in infancy and reduces obesity risk in later life by about 20%, presumably partly due to the lower protein supply with human milk than conventional infant formula. In a large randomized clinical trial, we tested the hypothesis that reduced infant formula protein contents lower insulin-releasing amino acid concentrations and thereby decrease circulating insulin and IGF-I levels, resulting in lesser early weight gain and reduced later obesity risk (the 'Early Protein Hypothesis'). The results demonstrate that lowered protein in infant formula induces similar – but not equal – metabolic and endocrine responses and normalizes weight and BMI relative to breastfed controls at the age of 2 years. The results available should lead to enhanced efforts to actively promote, protect and support breastfeeding. For infants that are not breastfed or not fully breastfed, the use of infant formulas with lower protein contents but high protein quality appears preferable. Cows' milk as a drink provides high protein intake and should be avoided in infancy.

Growth and development are key characteristics of childhood and sensitive markers of health status and adequate nutrition. Pediatricians regularly monitor the growth patterns of children as part of standard routine care, usually by plotting repeated growth measures over time on percentile reference curves to derive longitudinal growth patterns. Traditionally, this approach served primarily to early detect growth faltering as a marker of the presence of infectious and other diseases, or of inadequate nutrition, which show particularly rapid adverse effects on growth in infancy and early childhood [1]. More recently, however, the impact of excessive growth on child health has been receiving increasing attention [2–4].

In 1989, Karlberg [5] described the Infancy-Childhood-Puberty Growth Model (ICP model) of growth, and proposed the key drivers of growth to be age dependent. Karlberg concluded that pubertal growth is primarily driven by sex hormones, whereas prepubertal growth is regulated primarily by human growth hormone (hGH) acting through the release of insulin-like growth factor-I (IGF-I). In addition, dietary factors and especially the intakes of energy and protein are very important regulators of serum IGF-I concentrations and its biological activity, especially during the first months of infancy [6]. Amino acids were also reported to be more potent stimulators of IGF-I release than glucose [7]. For example, studies in 4-week-old rats showed that feeding a diet with 15 instead of 5% protein for only one week increased serum IGF-I more than 4-fold [8]. With increasing age of the child, there appears to be a gradual transition to a more important role of hGH in the regulation of IGF-I, along with increasing concentrations of growth hormone-binding proteins that are considered to reflect hGH receptor numbers [9, 10]. Nutrition also markedly influences insulin secretion which has key regulatory roles for anabolic pathways as well as tissue and lipid deposition during early growth [11, 12]. Glucose concentration is a key driver of insulin secretion, but the glucose-induced insulin secretion was shown to be markedly attenuated by a low protein supply [13]. Amino acids such as leucine also enhance insulin secretion via both acute effects, such as activated glutamate dehydrogenase activity, and chronic effects such as gene transcription and regulation of β-cell metabolism [14].

One pathway though which nutrients as well as the growth factors insulin and IGF-I can effectively modulate growth and metabolism is the mammalian target of rapamycin (mTOR), a highly conserved Ser/Thr kinase present in two structurally and functionally distinct complexes [15]. The mTORcomplex 1 (mTORC1) contains mTOR, mLST8, and raptor, whereas mTORC2 is composed of mTOR, mLST8, rictor, mSIN1, and PRR5. The growth factors insulin and IGF-I stimulate mTORC2 via an unknown pathway, and mTORC1 via PI3K and Akt inducing the mTORC1 activator Rheb [15]. Amino acids enhance ATP loading of RAG proteins and RAG-GTPases, which interact with Rheb and activate mTORC1 [15]. Of importance, full activation of mTORC1 is only achieved through the synergistic action of both growth factors and amino acids, while a low energy supply downregulates mTORC1 [15]. Thus, this pathway represents an elaborate sensor

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system by which nutritional supply regulates metabolism and growth. The enormous power of this system is demonstrated, for example, in mice with knockout of raptor in adipose tissue, which leads to disruption of mTORC1. These mice are lean and resistant to diet-induced obesity, and they have improved metabolic characteristics such as better glucose tolerance and insulin sensitivity, as well as resistance to diet-induced hypercholesterolemia [16]. These observations lead us to the conclusion that regulation of mTORC1 signaling by amino acids controls whole-body energy metabolism, bodyweight and body composition. Therefore, the current knowledge on the physiological mechanisms regulating metabolism, growth and related outcomes relevant for health indicate the large potential that improved nutritional practice during early life can have on long-term disease prevention and well-being, a concept widely known as early nutritional programming of life-long health [17–23]. Results of a recent randomized intervention trial in human infants demonstrate the powerful effects of modifying protein supply on metabolic and endocrine response as well as growth [24].

Postnatal Diet, Growth Patterns, and the Later Risk of Obesity and Related Non-Communicable Diseases

In early systematic studies performed already in the 1960s, McCance and Widdowson [25] demonstrated programming effects of food restriction for 3 weeks in the early life of animals which led to permanent reduction of bodyweight up to adulthood, whereas no such permanent effects were induced when the same degree of food restriction was induced at a later age. In humans, such postnatal programming effects on later body size have also been reported [26]. Both high birthweight and high weight gain in the first 2 years of life are associated with increased risk for later obesity, as reviewed in Koletzko et al. [27]. For example, we found early growth patterns predictive of overweight risk at school age in a study on 4,235 German children aged 5–6 years that were participating in the obligatory school entry health examination in Bavaria, Germany. Data on early gains of weight, length, body mass index (BMI) and Ponderal Index were derived from the measurements taken during the preventive health care checks offered to all children at birth, 6, 12 and 24 months [28]. Overweight at school entry was assessed according to gender- and age-specific BMI cutoff points. Among all the anthropometric measures and time intervals assessed, weight gain from birth to age 2 years was the best predictor of overweight at school age. Similarly, many studies in other populations also found early rapid weight gain associated with an increased risk of later obesity. Several recent systematic reviews on observational studies concluded that rapid weight gain in infancy and the first 2 years of life is a significant risk indicator for later adiposity [29–32].

Figure 1 shows the increased odds of later obesity during different age categories from childhood to adulthood predicted by early rapid weight gain, defined as

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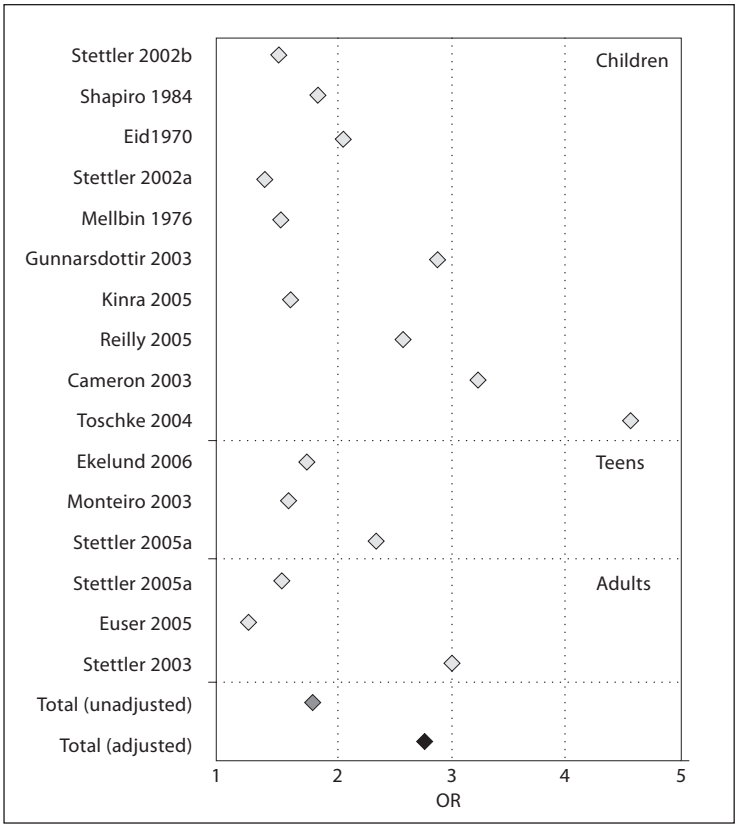

Fig. 1. Rapid weight gain in infancy or the first 2 years of life, defined as an increase in weight-for-age SDS >0.67 SD, is associated with increased odds of obesity in children, teenagers and adults. Redrawn from Adair [33] based on data in Baird et al. [29].

an increase in weight-for-age standard deviation score (SDS) >0.67 SD [29, 33]. In addition to an increased obesity risk, high early weight gain in the first 1–2 years of life is associated with a variety of other later adverse health outcomes [34–36] such as increased risk of high blood pressure [37], increased body fat deposition [28, 38, 39], less favorable lipoprotein profiles [40], diabetes [41] and asthma [42–44].

Protective Effects of Breastfeeding on Obesity Risk in Later Life

Populations of breastfed infants grow somewhat differently from formula-fed populations. In poor populations challenged by high rates of infection and diarrhea, the protective effects of breastfeeding against infectious gastroenteritis reduces growth faltering and can thus lead to higher mean weight gains of breastfed babies than of infants not receiving human milk [45–47]. With

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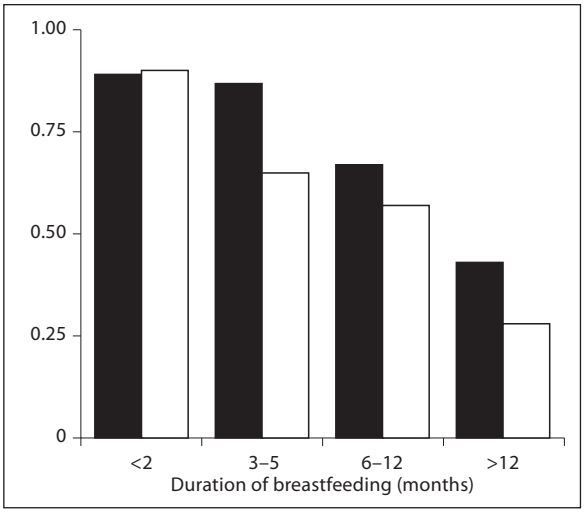

Fig. 2. In a cross-sectional study in >9,000 Bavarian children at school entry, longer duration of breastfeeding after birth (months) was associated with increasingly reduced odds of overweight (black) and obesity (white). Drawn from data of von Kries et al. [51].

adequate hygienic conditions, however, infants fed conventional infant formula achieve a greater gain of bodyweight and weight-for-length during infancy and early childhood than breastfed infants [48, 49]. In a systematic review of 19 studies in affluent populations, the cumulative difference in bodyweight was as large as 400 g at one year of age in infants breastfed for 9 months, and even 600–650 g in infants breastfed for 12 months [50].

Given these marked differences in early growth pattern, we explored the potential effects of these early growth differences on later body size. We studied the relation of breastfeeding with later overweight and obesity risk in a cross-sectional survey in Bavaria, Germany [51]. Data on height and weight were obtained for 9,357 children participating in the obligatory school health examination. Previously breastfed children showed a lower prevalence of both overweight (9.2 vs. 12.6%) and obesity (2.8 vs. 4.5%) than formula-fed ones. Differences in social class or lifestyle did not explain the protective effect of breastfeeding. Children who had ever been breastfed showed a significantly reduced adjusted odds ratio (OR) for both overweight (OR 0.79, 95% CI: 0.68–0.93) and obesity (OR 0.75, 95% CI: 0.57–0.98) as compared to those who were never breastfed. The adjusted ORs showed a significant inverse dose-response relationship between duration of breastfeeding and both overweight and obesity, which is compatible with a causal effect of breastfeeding or breast milk components on obesity reduction (fig. 2).

Many other investigators also explored the relationship between breastfeeding and later obesity in different cohort studies. These have been evaluated in

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several systematic reviews and meta-analyses [45, 46]. We performed a meta-analysis of published epidemiological studies (cohort, case-control or cross-sectional studies) that included only studies adjusting for at least three relevant confounding factors (birthweight, parental overweight, parental smoking, dietary factors, physical activity and socioeconomic status/parental education) and assessed obesity at an age between 5 and 18 years [52]. Included were 9 studies with more than 69,000 children. The result of the meta-analysis showed breastfeeding associated with a significant reduction of the risk of obesity in childhood in the fixed model (adjusted OR 0.78, 95% CI: 0.71–0.85). A dose-dependent effect of breastfeeding duration on the prevalence of obesity was reported in 4 of the 9 studies. Funnel plot regression gave no indication of publication bias. Very similar results were published one year later by Harder et al. [53] in a meta-analysis with different inclusion criteria and a much larger number of studies evaluated. They found breastfeeding associated with reduced pooled adjusted OR for later obesity of 0.75 (95% CI: 0.68–0.82) and concluded that each additional month of breastfeeding resulted in 4% lower obesity prevalence at later ages. In a further meta-analysis, Owen et al. [54] confirmed a protective effect of breastfeeding in a meta-analysis based on an even larger number of studies that met their inclusion criteria but reported a smaller effect size (OR 0.87). In this analysis, 75% of the effect weight was contributed by a single large study from the US Women, Infants and Children program on low-income women and children [17]. This study included a specific US population with a high degree of mixed feeding that might have led to results which are not representative of other breastfed populations. A more recent cluster randomized study did cast doubt on the protective effect of breastfeeding on obesity risk. The trial had been performed in hospitals in Belarus that were either assigned to enhanced breastfeeding promotion, or to no active intervention [55]. Whereas the intervention achieved a significantly longer duration of breastfeeding, there was no effect on obesity prevalence at the age of 6.5 years. However, it is important to note that this trial did not have sufficient statistical power to answer the question of a protective effect of breastfeeding relative to formula feeding, because rates of breastfeeding were relatively similar in the intervention and control groups, and the prevalence of obesity was low in this population [56]. Of interest, Beyerlein and von Kries [56] and Beyerlein et al. [57] found evidence that breastfeeding reduces particularly the proportion of subjects with a high BMI at later ages, while having little effect on the mean BMI.

We conclude that the totality of the evidence shows breastfeeding associated with a moderate but consistent protective effect against later obesity. Clearly, these findings should encourage the promotion, protection and support of breastfeeding, and of ethical approaches to the marketing of breast milk substitutes such as infant formulas and follow-on formulas, which do not undermine breastfeeding [58, 59].

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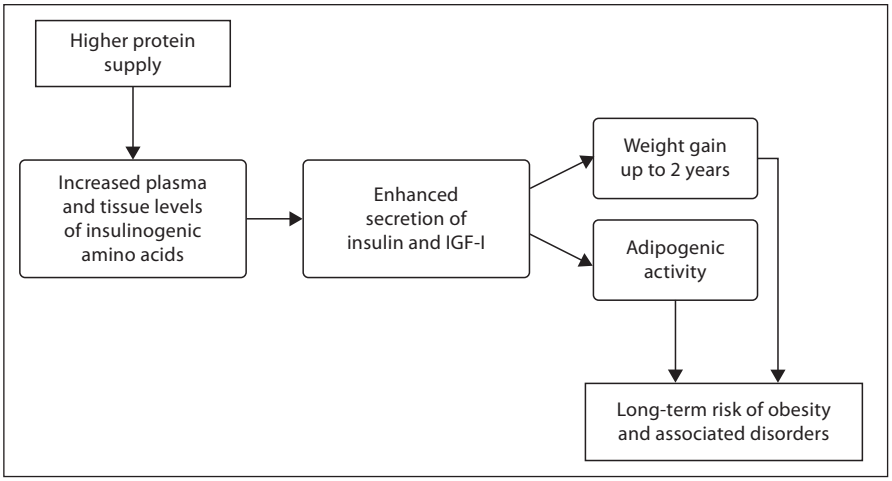

Fig. 3. The Early Protein Hypothesis suggests that a dietary protein supply to infants in excess of their metabolic requirements will lead to increased plasma and tissue concentrations of insulin-releasing amino acids and an enhanced secretion of insulin and IGF-I, which in turn will enhance early weight gain, adipogenic activity and long-term obesity risk. Redrawn after Koletzko et al. [23].

Mechanisms of Protective Effects of Breastfeeding: The 'Early Protein Hypothesis'

Understanding the underlying mechanisms as to how breastfeeding protects against later obesity could strengthen the conclusions on protective effects of breastfeeding, and it might help to extend protective effects to infants that are not breastfed for longer time periods by improving practices of feeding formula or complementary foods. Very many factors differ between breastfeeding and bottle feeding; therefore, numerous different hypotheses can be raised here [17].

We have previously proposed that the greater weight gain in formula-fed infants, relative to breastfed infants, is at least partly caused by the different intakes of metabolizable protein [50]. We explored the hypothesis that the usually 55–80% higher protein supply to formula-fed babies, as compared to breastfed infants [60, 61], could enhance both early weight gain and later obesity risk (the 'Early Protein Hypothesis') [62]. As described above, amino acids stimulate the secretion of insulin and IGF-I and positively activate mTORC1; thus, a high protein intake in excess of metabolic requirements may increase the concentrations of insulin and IGF-I in the circulation (fig. 3). Epidemiological studies actually found high protein intakes in infancy and the 2nd year, but not of energy, fat or carbohydrates, predictive of an early occurrence of the adiposity rebound and a high BMI in childhood [63–67].

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We tested the Early Protein Hypothesis in a randomized clinical trial, the European Childhood Obesity Project [24] performed as part of a European Commission-funded research collaboration [68]. This multicentric RCT was set up in study centers in five European countries (Belgium, Germany, Italy, Poland, Spain). Eligible for study participation were apparently healthy, term infants born from uncomplicated, singleton pregnancies. Formula-fed infants received exclusively one of the two randomized formulas at a mean age of 2 weeks after birth and no later than at the end of the 8th week of life. Breastfed children had to be exclusively breastfed for the first 3 months. Infant formulas were replaced by follow-on formulas from the 5th month of age onwards.

The lower protein (LP) and higher protein (HP) infant and follow-on formulas had an identical energy density achieved by adaptation of the fat content, whereas the protein contents were 1.8 g protein/100 kcal versus 2.9 g protein/100 kcal in the infant formulas and 2.2 g protein/100 kcal versus 4.4 g protein/kcal in the follow-on formulas (table 1). The relative contents of amino acids did not differ between all four formulas, e.g. branched-chained amino acids made up 23% of the protein content in all four formulas (table 1).

A reference group of 619 breastfed infants was recruited, of whom 298 children could be followed until the 24 months visit. Complete anthropometric follow-up data at 24 months were available for 313 LP infants (follow-up rate = 58%) and 323 HP infants (59%). The median age at the baseline visit was 16 days (interquartile range, IQR: 2–29 days). The protein intake was significantly different between the two formula groups at all time points up to 12 months of age but not thereafter. The difference ranged between 5.5 g per day (95% CI: 5.1–5.9) in the first month to 8.5 g (7.8–9.3) at 6 months. Energy intake in the LP and HP formula groups was identical at 3, 12, and 24 months, but was slightly higher (24 kcal, 95% CI: 6–43) at 6 months of age in the LP formula group.

Differences in weight and weight-for-length between the formula groups emerged at 6 months of age and remained relatively stable thereafter with a decreasing tendency towards the end of the study. At 24 months of age, length was not different between the intervention groups. The mean weight attained at 24 months was 12.42 and 12.60 kg for the LP and HP groups, respectively. HP led to a significantly higher BMI than LP during the intervention period from 6 months onwards as well as after the end of the intervention (fig. 4). Of interest, the BMI in the LP group was identical to the breastfed group at 2 years of age. The effect of the intervention was not different among the countries for any of the analyzed anthropometric measures. In addition to total body growth, also a significant effect on kidney growth was found [69]. We estimated the potential impact of the reduced protein intake in infancy on obesity in adolescence based on the observed effects of change in weight-for-length gain during the first 2 years of life on later obesity in large prospective cohort studies, and we calculated an expected reduction of obesity prevalence

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Table 1. Macronutrient and amino acid content of study formulas with LP and HP used in the European Childhood Obesity Trial

	Infant formula		Follow-on formula	
	LP	HP	LP	HP
Energy, g/100 ml	69.9	69.8	72.7	72.5
Proteins, g/100 ml	1.25	2.05	1.6	3.2
Percent energy	7.1	11.7	8.8	17.6
Lipids, g/100 ml	3.9	3.5	4.0	3.3
Carbohydrates, g/100 ml	7.5	7.5	7.6	7.6
Amino acids				
Glutamic acid, mg/100 ml	286	473	369	738
Proline, mg/100 ml	135	223	174	348
Leucine, mg/100 ml	119	197	154	308
Lysine, mg/100 ml	94	155	121	243
Asparagine, mg/100 ml	89	147	115	230
Valine, mg/100 ml	84	139	108	216
Isoleucine, mg/100 ml	77	128	100	200
Serine, mg/100ml	71	118	92	184
Tyrosine, mg/100 ml	62	103	80	161
Phenylalanine, mg/100 ml	58	97	75	151
Threonine, mg/100 ml	56	92	72	144
Arginine, mg/100 ml	50	74	57	115
Alanine, mg/100 ml	42	69	54	108
Histidine, mg/100 ml	32	53	41	82
Glycine, mg/100 ml	24	40	31	62
Tryptophane, mg/100 ml	22	29	23	46
Cystine + methionine, mg/100 ml	40	66	52	103

Adapted from Koletzko et al. [24] and Socha et al. [71].

at 14–16 years by 13% [24]. The actual effects of the intervention after the early toddler age are currently being explored in a longer term follow-up study.

Biochemical and Endocrine Markers

To explore our underlying hypothesis that the effect of dietary protein on growth and obesity risk is mediated by amino acid concentrations, insulin and IGF-I, we performed respective analyses in venous blood and in urine samples that were obtained from participating infants at the age of 6 months and were analyzed in one central laboratory [70].

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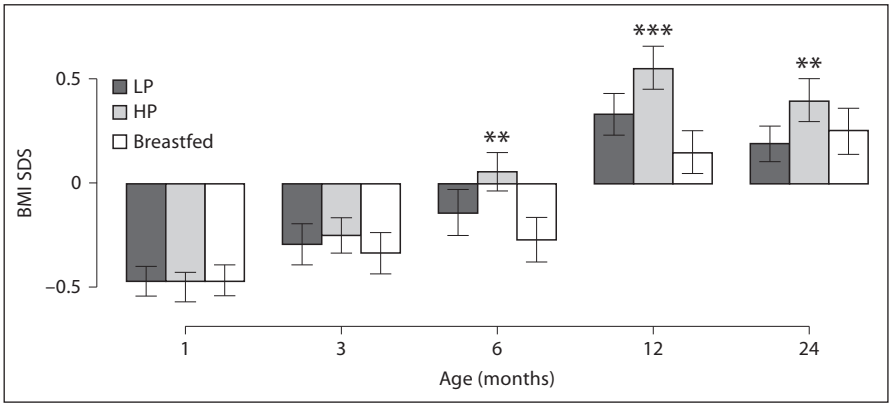

Fig. 4. BMI SDS from birth to age 2 years in subjects participating in the European Childhood Obesity Project fed breast milk, or randomized to receive for the first year of life formulas with LP or HP contents. Formula-fed infants in the HP group showed higher BMI values than breastfed infants in infancy and at 2 years of age. The group randomized to LP had significantly lower BMI levels than the HP group, and LP normalized BMI levels at age 2 years as compared to breastfed subjects. Drawn from data of Koletzko et al. [24].

Median total amino acid serum concentrations were slightly higher in the HP group (3,041 μmol/l, IQR 2,679–3,394) than in the LP group (2,841 μmol/l, IQR 2,523–3,186, $p < 0.001$). Particularly large group differences were found for the branched-chain amino acids valine (+42% in HP), leucine (+37%) and isoleucine (+32%; table 2). The concentrations of all other essential amino acids were at least 10% higher in HP than in LP. In contrast, non-essential amino acids were either not different or even lower in the HP group, with the exception of tyrosine and asparagine which were both significantly higher. Interestingly enough, the total non-essential amino acid concentrations were not higher but significantly lower in the HP group ($p = 0.001$) [70].

Serum urea concentrations were significantly higher in infants fed HP than in those fed LP formulas (table 3). In the HP group, the serum concentrations of total IGF-I and free IGF-I were about 40% higher than in the LP group (table 3), while IGF-BP2 concentrations were about 30% lower. The HP group also showed a higher urinary C-peptide concentration and C-peptide/creatinine ratio, indicating enhanced insulin secretion, as well as a significantly lower serum glucose concentration (table 3).

Both formula groups showed differences to the breastfeeding group. Generally, parameters of the IGF axis, C-peptide and amino acids were more similar between the LP group and the breastfed group. Total IGF-I, free IGF-I, and IGF-BP3 levels were all significantly lower – up to almost 60% – in the breastfed than in the formula groups (table 3) [70]. Serum glucose, urinary C-peptide and the C-peptide/creatinine ratio all differed significantly between

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Table 2. Serum amino acid (AA) concentrations in infants aged 6 months fed HP and LP formula, and in breastfed infants (BF)

	LP	HP	p value (HP vs. LP)	BF
Essential amino acids				
ILE, µmol/l	64 (50, 80)[a]	85 (62, 114)[f]	<0.001	58 (46, 74)
LEU, µmol/l	120 (98, 143)[b]	165 (124, 212)[f]	<0.001	106 (90, 133)
LYS, µmol/l	166 (134, 197)[c]	197 (156, 248)[f]	<0.001	145 (121, 184)
MET, µmol/l	31 (26, 39)[c]	35 (26, 46)[f]	<0.001	27 (22, 35)
PHE, µmol/l	72 (61, 83)[c]	84 (70, 100)[f]	<0.001	61 (48, 74)
THR, µmol/l	126 (101, 154)	142 (118, 173)[f]	<0.001	119 (92, 150)
TRP, µmol/l	56 (47, 67)[b]	67 (54, 82)[f]	<0.001	60 (50, 74)
VAL, µmol/l	214 (182, 247)[c]	304 (241, 376)[f]	<0.001	172 (143, 208)
Non-essential amino acids				
ALA, µmol/l	440 (346, 526)	420 (349, 517)	0.304	430 (355, 495)
ARG, µmol/l	115 (97, 137)	110 (91, 128)	0.038	113 (91, 129)
ASN, µmol/l	54 (45, 64)	58 (47, 68)[e]	0.015	52 (45, 64)
ASP, µmol/l	25 (17, 35)	27 (19, 35)	0.143	26 (18, 38)
GLN, µmol/l	605 (542, 683)[c]	556 (490, 613)[f]	<0.001	664 (573, 748)
GLU, µmol/l	122 (95, 168)	115 (88, 172)	0.179	130 (90, 193)
GLY, µmol/l	267 (217, 319)[c]	230 (199, 273)[d]	<0.001	220 (185, 264)
HIS, µmol/l	105 (88, 123)[c]	107 (93, 124)[f]	0.215	88 (74, 105)
SER, µmol/l	161 (138, 194)[c]	159 (140, 189)[f]	0.750	187 (156, 207)
TYR, µmol/l	83 (70, 103)[c]	101 (76, 125)[f]	<0.001	66 (54, 80)

Adapted from Socha et al. [71]. Values are expressed as median (IQR, 25th, 75th quartile).
[a] $p < 0.05$, LP vs. BF; [b] $p < 0.01$, LP vs. BF; [c] $p < 0.001$, LP vs. BF; [d] $p < 0.05$, HP vs. BF;
[e] $p < 0.01$, HP vs. BF; [f] $p < 0.001$, HP vs. BF.

the breastfed and the formula groups (table 3). Essential amino acids, especially branched-chain amino acids, were lower in the breastfed than in the LP group, whereas non-essential amino acids had about the same level.

Total IGF-I was found positively correlated with weight-for-length at 6 (fig. 5), 12, and 24 months, whereas C-peptide showed no association with weight-for-length.

Conclusions

Breastfeeding or formula feeding and dietary protein supply in infancy were found to markedly affect the metabolic and endocrine response of infants, and their growth. HP intakes increase the plasma levels of essential amino acids, especially branched-chain amino acids, serum concentrations of total and

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Table 3. Serum concentrations of free and total IGF-I IGF-BP2 and IGF-BP3, glucose and urea, and of urinary C-peptide in infants on LP and HP and in BF infants

Parameter	LP	HP	P (HP vs. LP)	BF
IGF-I free, ng/ml	0.43 (0.27, –0.77)[a]	0.60 (0.34, 1.11)[b]	<0.001	0.31 (0.21, 0.48)
IGF-I total, ng/ml	34.7 (17.7, 57.5)[a]	48.4 (27.2, 81.8)[b]	<0.001	14.1 (5.1, 33.2)
IGF-BP2, ng/ml	1,090 (865, 1,438)	765 (575, 1,013)	<0.001	1,370 (1,055, 1,740)
IGF-BP3, ng/ml	2,908 (2,449, 3,440)	2,969 (2,538, 3,483)	0.248	2,454 (1,984, 2,794)
C-peptide/ creatinine ng/mg	107.3 (65.2, 194.7)[a]	140.6 (80.0, 203.8)[b]	0.030	57.0 (27.3, 119.3)
C-peptide, ng/ml	19.5 (9.4, 34.6)[a]	26.9 (13.3, 45.6)[b]	0.002	9.3 (3.5, 20.1)
Glucose, mg/dl	85 (77, 93)	83 (77, 89)[b]	0.022	86 (79, 93)
Urea, mg/dl	18 (14, 21)[a]	29 (20, 36)[b]	<0.001	11 (8, 16)

Adapted from Socha et al. [71]. Values are expressed as median (IQR, 25th, 75th quartile).
[a] $p < 0.001$, LP vs. BF; [b] $p < 0.001$, HP vs. BF.

free IGF-I, and urinary C-peptide levels which reflect increased insulin secretion, while the serum glucose level was lowered. Using infant formula with LP content results in a more similar – but not equal – metabolic and endocrine response as compared to breastfed infants, while it normalizes weight and BMI of formula-fed babies relative to healthy breastfed subjects during the first 2 years of life.

The observed marked effects of formula protein contents on total and free IGF-I agree with earlier observations of lower IGF-I levels in breastfed compared to formula-fed infants, and in some studies with varying protein intakes, as reviewed by Socha et al. [71]. The observed correlation of IGF-I levels with weight-for-length leads us to conclude that IGF-I is a key driver of weight gain during infancy, which clearly can be modulated to a biologically relevant extent by dietary composition. In addition to modulating growth, elevated IGF-I levels in infancy may also have further long-term effects. Formula feeding, HP intakes, and higher IGF-I levels in infancy have been associated with lower IGF-I levels in later life [72–75], whereas breastfeeding is associated with lower IGF-I in infancy but higher IGF-I in later childhood [72]. In healthy adults, a lower IGF-I concentration has been associated with an increased risk of both ischemic heart disease and diabetes [76] as well as with increased incidence of malignancies such as prostate and breast cancer [77]. Therefore, programming of the IGF-I axis through early nutrition in infancy may have a considerable impact on the later risk not only of obesity but also of other

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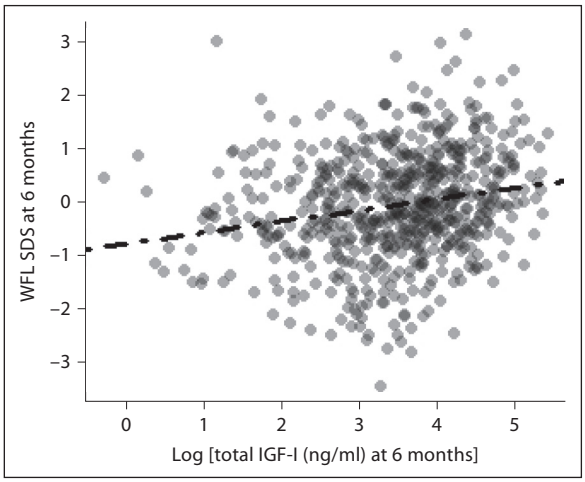

Fig. 5. At the age of 6 months, total IGF-I (log scale) is a significant predictor of weight-for-length (WFL) SDS in 513 infants participating in the European Childhood Obesity Trial (rho = 0.24, $p < 0.001$). Drawn from data of Socha et al. [70].

adult diseases [72]. While lowering protein supply decreased IGF-I levels, these still remained far higher than the levels observed in breastfed babies. Thus, further exploration of the regulators of the IGF-I axis in early life is needed, including the investigation of the effects of IGF gene variants on IGF-I and its binding proteins, and their interaction with nutrition and growth.

Given that insulin plays a central role in metabolic regulation, IGF-I transcription and enhanced body fat deposition, the observed increased C-peptide levels by HP intake might also induce lasting effects on growth and health outcomes. Attenuation of the elevated insulin secretion though optimized early nutrition, such as LP intake in formula-fed babies, seems desirable. In addition to reducing protein supply with infant formula, the use of unmodified cows' milk as a drink during the first year of life, which provides very high protein intake, should be discouraged [78].

The available data should prompt enhanced efforts to actively promote, protect and support breastfeeding. For those infants that are not breastfed or not fully breastfed, we consider the use of infant formulas with reduced protein content but high protein quality preferable.

Appendix

The European Childhood Obesity Project Study Group

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