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An exploratory study of clinical factors associated with IGF-1 and IGFBP-3 in preterm infants

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Abstract

BACKGROUND: Despite advances in parenteral nutrition, postnatal growth failure in very low birthweight (VLBW) preterm infants is common and associated with chronic health problems. Insulin-like growth factor 1 (IGF-1) is positively associated with improved infant growth, but factors which promote IGF-1 levels in this population have not been clearly identified. The objective of this study was to explore early factors that influence IGF-1 in VLBW preterm infants.

METHODS: VLBW infants were enrolled into a prospective, randomized controlled nutrition trial ($N = 87$). Outcome measures included IGF-1 and IGFBP-3 levels measured at 35 weeks PMA. Linear regression analyses tested the relationships between candidate clinical predictors and levels of IGF-1 and IGFBP-3.

RESULTS: Higher protein intake, longer duration of parenteral nutrition, and lower IGFBP-3 levels at 1 week of life were associated with lower IGF-1 levels at 35 weeks PMA. Neither early markers of insulin resistance nor degree of illness were associated with IGF-1 levels at 35 weeks PMA.

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AUTHOR CONTRIBUTIONS

S.E.R. conceived and designed the study. E.M.N., J.D.G.V. and M.E.P. performed data acquisition. N.M. analyzed data. All authors interpreted data. M.E.P. and N.M. drafted the manuscript, tables, and figures. All authors critically revised the manuscript, approve submission of manuscript for publication, and agree to be accountable for all aspects of the work.

COMPETING INTERESTS

The authors declare no competing interests.

CONSENT STATEMENT

Parents of patients were required to provide informed consent to participate in this study.

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CONCLUSION: Optimization of early nutrient intake, and attention to route of delivery, may have a lasting influence on IGF-1/IGFBP-3, and in turn, long-term health outcomes.

INTRODUCTION

Postnatal growth failure, defined as body weight or length below the 10th perentile of expected intrauterine growth at time of hospital discharge,[1] occurs in up to 50% of very low birthweight (VLBW) preterm infants[2] and is associated with a myriad of chronic health problems later in life including obesity, metabolic syndrome, and intellectual disability.[3] Postnatal growth failure has been partially attenuated in the VLBW population through advances in perinatal nutrition, especially enhanced parenteral nutrition during the first two weeks of life.[4–7] Despite these advances, postnatal growth failure remains common in the VLBW population. Perturbations in the maturation of normal endocrine homeostatic mechanisms offers one potential explanation for persistent postnatal growth failure in this population.

Insulin-like growth factors (IGFs) are critical regulators of growth and organ development.[8] Prenatal IGF-mediated growth is predominately regulated by the maternal-placenta unit as the fetal endocrine organs mature. Postnatally, IGFs continue to play a primary role in regulation of linear growth in preterm infants. Notably, VLBW preterm infants have 80% lower IGF-1 compared to their term counterparts.[9] Thus, early nutritional and hormonal programming of the IGF system may be a key mediator in the link between birthweight, postnatal growth, and long-term metabolic disease.[8,10]

Insulin-like growth factor binding proteins (IGFBPs) regulate the bioavailability of IGF-1.[11] Six types of IGFBPs have been identified in humans, of which IGFBP-3 is the most prevalent.[9] In preterm infants, IGFBP-3 is positively associated with greater postnatal growth during the first two years of life.[8,12,13] 80–95% IGF-1 is bound to IGFBP-3 as a circulating complex with the acid-labile subunit. Thus, bioavailable free IGF-1 is dependent on both its rate of hepatic production as well as its delivery and release by IGFBP-3 at target tissues.[9] External influences on the regulation of IGFBP-3 levels in preterm infants are not well established.

The objective of this study was to explore associations between early clinical factors and IGF-1/IGFBP-3 levels in VLBW infants. We hypothesized that intrauterine growth, nutrition, early metabolic variables, and degree of illness among VLBW premature infants, would be associated with IGF-1 and IGFBP-3 levels.

METHODS

Data for this exploratory analysis were obtained during a randomized clinical trial of VLBW preterm infants admitted to the University of Minnesota Masonic Children's neonatal intensive care unit (NICU) between 2017 and 2019 (Clinical Trial No NCT03238768; https://clinicaltrials.gov/ct2/show/NCT03238768).[14] Preterm infants born between 22 weeks and 0 days gestational age and 31 weeks and 6 days gestational age, with a birthweight of less than 1500 g, were included in the study. Infants diagnosed prenatally with a condition other than prematurity known to affect growth, adiposity, or neurocognitive development

were excluded. After receiving appropriate parental consent, patients were randomized 1:1 within the first 12 h of life to early standard parenteral nutrition (control, average of 431 total kcals/week) or enhanced parenteral nutrition (intervention, average of 547.5 total kcals/week) for the first week of life. Further details on recruitment, study design, primary and secondary outcomes are published elsewhere.[14,15]

Early IGF-1 and IGFBP-3 levels were defined as measurements obtained at 1 week of life. Late IGF-1 and IGFBP-3 levels were defined as measurements obtained at 35 weeks postmenstrual age (PMA). The 35 week PMA timepoint was chosen per clinical trial protocol to allow consistency in PMA at measurement and capture as many infants as possible prior to NICU discharge. Additionally, since lab draws are less frequent after 35 weeks, families were not asked to consent to additional non-clinical lab draws. Ethical approval for this trial was approved by the University of Minnesota Institutional Review Board (#00000063).

A total of 90 infants were enrolled from an eligible population of 203 VLBW preterm infants meeting entry study criteria during the recruitment period (Fig. 1). 45 infants (50%) were randomized to the control group and 42 (46%) to the intervention group. Three infants were excluded from the study due to death ($n = 1$), metabolic disorder ($n = 1$), and incomplete data prohibiting analysis ($n = 1$).

Data collection

Glucocorticoid administration, birth anthropometrics, infant sex, race, gestational age at birth, insulin administration, and nutritional intake were all collected from the electronic medical record. Duration of parenteral nutrition was defined as the duration between initation of parenteral nutrition and the day of life (DOL) when full enteral feeds were achieved. The degree of illness at DOL 1 was assessed using the Score for Neonatal Acute Physiology (SNAP).[15] Neonatal morbidities of hypoglycemia, hyperglycemia, hypertriglyceridemia, inflammation, and intraventricular hemorrhage (IVH) were extracted from the electronic medical record. Hypoglycemia was defined by experiencing at least one blood glucose (BG) measure of <40 mg/dL, hyperglycemia as one BG > 180 mg/dL, hypertriglyceridemia as one triglyceride (TG) level >300 mg/dL, and inflammation by c-reactive protein (CRP) level (measured as a continuous variable).

Early and late IGF-1 and IGFBP-3 levels were measured from serum related to routine lab work. IGF-1 was analyzed by Quest Diagnostics using high-resolution liquid chromoatography/mass spectrometry (test code 16293, interassay CV < 5%). Reference normative values for <1 year of age in males are 14–142 ng/mL and in females 17–185 ng/mL. IGFBP-3 was analyzed by the Fairview Clinical Laboratory using enzyme-labeled chemiluminescent immunometric assay (Siemens Immulite 2000, Siemens Healthcare Diagnostics, interassay CV < 6%). Reference normative values for <1 year of age are 0.7–3.6 mcg/mL. BG and TG levels were monitored per standard NICU and nutrition protocols.

Insulin was delivered at the discretion of the neonatologist for hyperglycemia per current NICU protocol. CRP levels were obtained at the discretion of the neonatologist when there

was a clinical concern for early onset sepsis. Detailed nutritional intake was recorded daily throughout the NICU hospitalization by the NICU dietitian.

Statistical analysis

Patient demographics and clinical characteristics were summarized as means and standard deviations for continous factors, and frequencies and percentages for categorical factors. Univariate associations between early and late IGF-1 and IGFBP-3 were analyzed using linear regression models. Associations between candidate predictors and late IGF-1 and IGFBP-3 levels were assessed separately using linear regression models adjusted for infant gestational age at birth, PMA at time of lab draw, sex, and study arm. A mediation analysis using the Baron-Kenny procedure[16] was conducted assessing mean parenteral protein intake in the first week of life as a potential mediator for the relationship between clinical factors and early IGFBP-3 and late IGF-1 with significance determined via Bootstrap. All analyses were conducted at the 0.05 siginificance level using the R software version 4.2.0.[17]

RESULTS

Baseline demographic characteristics, hormone levels, anthropometrics, nutritional intake, and comorbidities are summarized in Table 1. The cohort represents patients equally distributed between randomized study arm and sex. The majority of the cohort was white (65%) and received antenatal steroids (90%). The mean gestational age of the cohort was 27 weeks and 1 day of age with an average birth weight of 942.9 g. Of the 87 infants included in this cohort, 86% had IGF-1 level at DOL 7 and 71% at 35 weeks PMA. 89% of infants had an IGFBP-3 level at DOL 7 and 76% at 35 weeks PMA. Patients without routine lab draws at study timepoint or without an adequate amount of serum had missing lab values.

During the first week of life, the majority of calorie (76%) and protein (83%) intake was from parenteral nutrition (PN) in all participants (Table 1). No hypoglycemia occured. 25% of infants experienced hyperglycemia of which 58% were treated with insulin. For all enrolled infants, protein comprised 16% of caloric intake during the first week of life.[14] Infants randomized to standard PN (control) received 8% lower caloric intake compared to the enhanced PN (intervention) group.[14] There were no other differences in variables measured between control and intervention groups.[14]

Relationships between early IGF-1/IGFBP-3 levels, somatic growth at NICU discharge, and body composition at NICU discharge in VLBW infants are summarized in Table 2. Neither early IGF-1 nor IGFBP-3 predicted growth or body composition with the exception of late IGFBP-3 levels and infant length at NICU discharge (positively associated). The relationship between early and late IGF-1 or IGFBP-3 are reported in Supplemental Fig. 1 and Table 2 respectively. Early IGFBP-3 levels were associated with IGF-1 and IGFBP-3 levels at 35 weeks PMA. Early IGF-1 levels were not associated with later IGF-1 or IGFBP-3 levels.

As we are interested in the potential of early IGF-1/IGFBP-3 levels as predictors of postnatal growth failure in VLBW infants we next explored relationships between early, established predictors of growth failure[6] and fetal regulators of IGF-1[11] in VLBW infants with early and late IGF-1/IGFBP-3 levels. Significant relationships are summarized in Fig. 2 with more

detailed descriptors in Supplemental Table 1. Parenteral protein intake during the first week of life was negatively associated with late IGF-1 levels. A longer duration of PN and higher total (parenteral + enteral) protein intake in the first week of life was associated with lower late IGF-1 and IGFBP-3 levels respectively.

There were no associations between parenteral calories, fat (intralipid emulsion) intake, or enteral protein intake and IGF-1 or IGFBP-3 levels. There were no associations observed between glucose, insulin, triglycerides, or cortisol, and IGF-1or IGFBP-3 levels (Supplemental Table 1). There were no associations between hyperglycemia and IGF-1 or IGFBP-3 levels. Degree of critical illness on day 1–2 of NICU stay was positively associated with IGFBP-3 levels at 1 week of life but no significant associations were observed between c-reactive protein and IGF-1 or IGFBP-3 levels.

Fig. 3 summarizes significant associations between early predictors of postnatal growth failure and late IGF-1/IGFBP-3 levels. Early IGFBP-3 level, early parenteral/total protein, and duration of parenteral nutrition were associated with late IGF-1 levels. To determine if early IGFBP-3 mediated the relationship between mean parenteral protein intake and late IGF-1 levels we performed a mediation analysis (Supplemental Table 2). There were significant associations between mean parenteral protein intake during the first week of life (74.71 ± 14.38, t value 5.19, $p < 0.01$) and late IGF-1 as well as mean parenteral protein during the first week of life (1.94 ± 0.27, t value −7.19, $p < 0001$) and early IGFBP-3. Mediation analysis model shows the effect of mean parenteral protein as moderately reduced (44.92 ± 19.43, t value 2.31, $p < 0.05$) indicating that early parenteral protein intake may mediate the relationship between early IGFBP-3 and late IGF-1, however the mediation effect was not significant [ACME −4.942 (−15.72, 0.59), $p = 0.20$].

DISCUSSION

In this exploratory study we measured relationships between *inutero* growth, nutritional intake, metabolic exposures, and degree of illness during the first week with IGF-1 and IGFBP-3 levels in preterm VLBW infants. The major findings of this study are that lower protein intake, shorter duration of parenteral nutrition, and higher IGFBP-3 levels during the first week of life was associated with higher IGF-1 levels at 35 weeks PMA. Based on these findings, we have generated two hypotheses to explain these observations and pave the way for future studies that could improve long-term health outcomes for preterm VLBW infants.

The first hypothesis generated from this study is that early IGFBP-3 levels predict long-term health outcomes in VLBW infants. This hypothesis is supported by our findings that early IGFBP-3 levels were associated with IGFBP-3 levels at 35 weeks PMA (0.56, 0.28–0.84; $p < 0.001$) and infant length at NICU discharge (1.1, 0.17–2.03; $p = 0.022$). Additionally, there was a trend towards association between early IGFBP-3 levels and infant length at NICU discharge (1.41, −0.16–2.99; $p = 0.078$). Since linear growth during the NICU course is associated with neurocognitive and respiratory outcomes long-term,[6,18,19] IGFBP-3 may mediate the relationship between linear growth and long-term health outcomes. To test this hypothesis a larger sample size powered to test IGFBP-3 as a mediating factor in these outcomes would be necessary.

Testing the hypothesis that early IGFBP-3 levels predict long-term helth outcomes in VLBW infants addresses an important knowledge gap in care delivery for preterm infants. The role of IGFBP-3 in somatic growth has not been fully characterized in the preterm population. Previous work, although limited, has focused mostly on the positive relationship between IGF-1 levels and linear growth in preterm infants.[9,11,13,20–22]

In this study we did not find a significant relationship between IGF-1 levels and linear growth. One previous prospective cohort study ($n = 29$) reported that IGFBP-3, but not IGF-1, levels predicted linear growth during the first 2 years of life for extremely preterm infants.[12] Both studies may differ from previous research findings due to inadequate power to detect a relationship. Alternatively, our study which measured IGF-1 at 35 weeks PMA may have been too early to detect a relationship between somatic growth and IGF-1. We do, however, report a strong direct relationship between early IGFBP-3 and late IGF-1. An important opportunity to investigate the strength of these relationships (i.e., IGF-1 and IGFBP-3, IGF-1 and long-term health outcomes, IGFBP-3 and long-term health outcomes) is to leverage ongoing clinical trials investigating ROP and BPD prevention with human recombinant IGF-1/IGFBP-3 in preterm infants.[23–26]

A second hypothesis generated from the findings of this study is that early protein intake is inversely associated with later IGF-1/IGFBP-3 levels. This hypothesis is supported by our results showing an inverse relationship between early parenteral protein and late IGF-1 (−14.47, −23.97 to −4.96; $p = 0.004$) as well as early total protein (parenteral + enteral) and late IGFBP-3 (−0.36, −0.59 to −0.12; $p = 0.003$). The inverse association between early protein exposure and later IGF-1/IGFBP-3 was contrary to our initial hypothesis based on previous studies demonstrating a positive association between these variables.[27–34]

A potential explanation for the observed relationship in this study is early parenteral protein exposure may suppress IGF-1 and/or IGFBP-3 secretion[35–37] Investigation aimed at reporting the longitudinal relationship between protein (parenteral + enteral) intake and IGF-1/IGFBP-3 levels would provide support to this hypothesis. Both pre-clinical animal models and large clinical studies are likely needed to best investigate this relationship and test these hypotheses. Expected outcomes from testing this hypothesis would include a better understanding of the relationships between early protein intake, linear growth, and IGF-1/IGFBP-3 in VLBW infants.

Testing the hypothesis that early protein intake is inversely associated with later IGF-1/IGFBP-3 levels addresses an important knowledge gap in nutrional management for preterm infants. Foremost, the current evidence for provision of parenteral protein greater than the standard 3–4 g/kg recommended by the Academy of Nutrition and Dietetics/European Society for Enteral and Parenteral Nutrition is sparse. Recent evidence from the ProVIDe Trial Group reports a postive relationship between higher protein intake and moderate-severe neurodisability at 2 years of age in extremely preterm infants ($n = 434$).[38] As both IGF-1 and IGFBP-3 are critical for the developing brain,[29,39,40] gaining an understanding of the complex relationships between protein intake, long-term neurodevelopment, and IGF-1/IGFBP-3 may inform best nutritional practices for preterm infants.

There are limitations to this study that affect interpretation and warrant further investigation. The most salient limitation is the small sample size in this study. While data from this cohort was collected prospectively, the study was not powered to find statistically significant associations between early environmental signals, IGF-1 and IGFBP-3 levels. Additionally, the small sample size of this study does not allow for stratified analysis to measure relationships regarding gestational age at birth, sex, nutritional deficits, or presence of intrauterine growth restriction which all may influence associations with IGF-1 and IGFBP-3 levels. Endocrine hormones such as insulin, cortisol, glucagon may also influence the complex relationships between early nutrition, postnatal growth, and IGF-1/IGFBP-3 but were not evaluated during this study. While this study included an early and late time point for IGF-1/IGFBP-3 analysis, the optimal time to determine the relationship between preterm somatic growth and IGF-1/IGFBP-3 remains not fully understood. Therefore, study of IGF-1/IGFBP-3 at 35 weeks PMA may not best characterize this relationship. Lastly, data was collected from a single institution's NICU with specific nutrition protocols potentially limiting the variability in practice.

In summary, early protein intake, parenteral nutrition duration, and early IGFBP-3 levels were associated with later IGF-1 levels. If replicated in a larger sample of VLBW preterm infants, the associations reported in this study corroborate that IGF-1 is nutritionally regulated in preterm infants, lending clinical equipoise for research that focuses on nutritional and endocrine strategies to prevent growth failure. Further investigation to better understand variables which are associated with IGF-1 and IGFBP-3 levels in preterm infants, as well as the mechanisms behind these relationships, may provide insight into the optimal composition of parenteral nutrition in addition to improving long-term health outcomes for infants born preterm.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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DATA AVAILABILITY

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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IMPACT:

- In very low birthweight preterm infants, early protein intake, duration of parenteral nutrition, and insulin-like growth factor binding protein 3 (IGFBP-3) levels at 1 week of life are positively associated with insulin-like growth factor 1 (IGF-1) levels at 35 weeks postmenstrual age.
- Data from this study highlight the influence of early nutrition on components of the endocrine axis in preterm infants.
- Strategies aimed at early initiation of enteral nutrition, as well as optimizing composition of parenteral nutrition, may bolster hormones involved in promoting preterm infant growth.

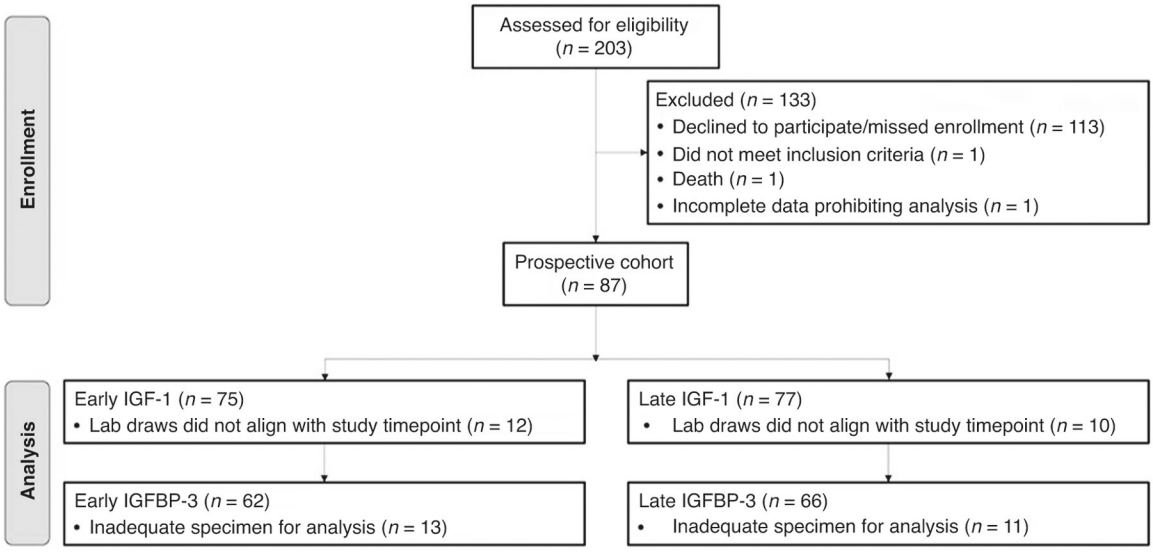

Fig. 1. CONSORT flow diagram.

IGF-1: Insulin-like growth factor 1, IGFBP-3: Insulin-like growth factor binding protein 3. IGF-1/IGFBP-3 levels obtained from blood samples. Early: Day of life 7, Late: 35 weeks postmenstrual age.

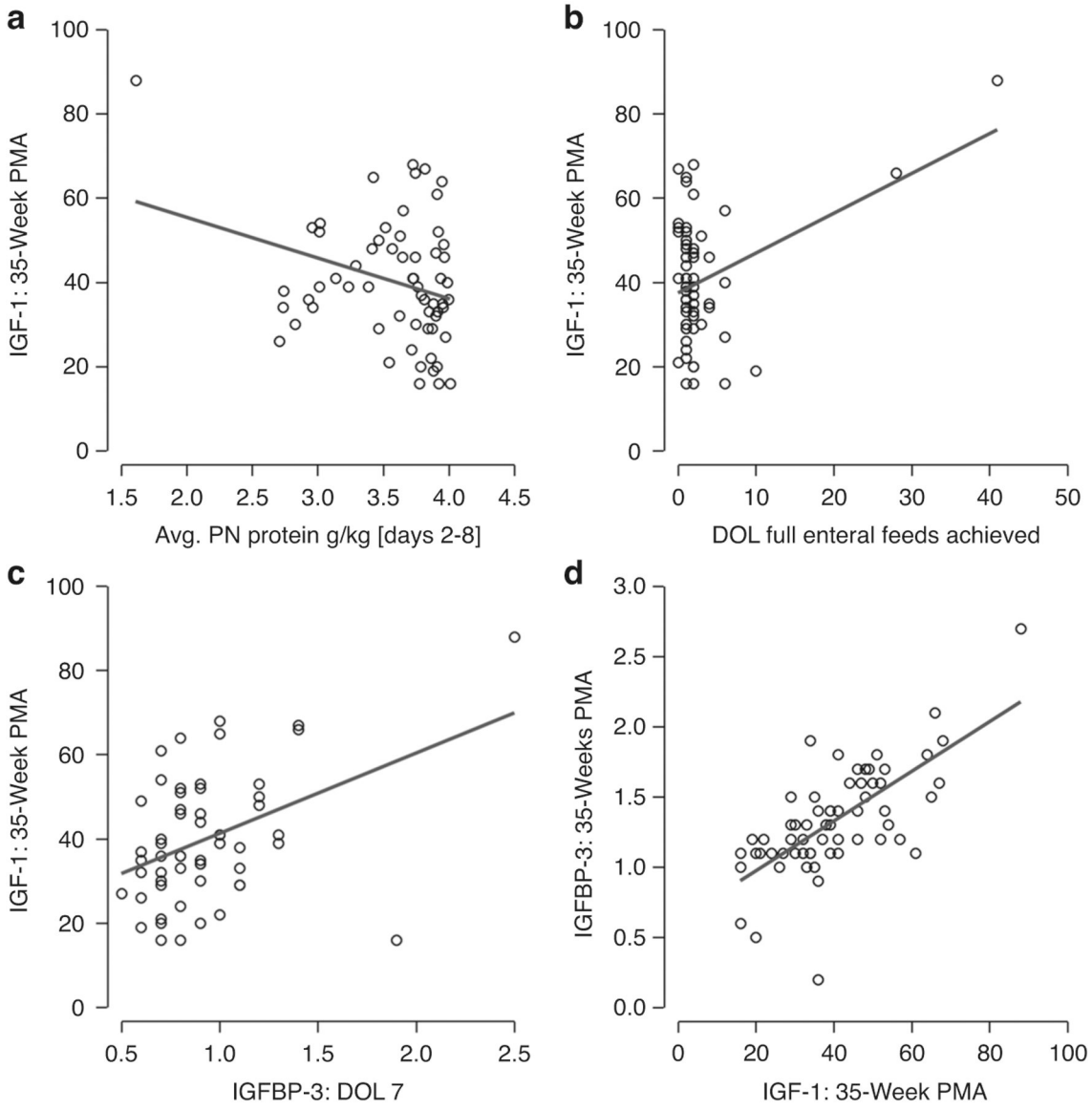

Fig. 2. Early parenteral protein and IGFBP-3 levels are associated with Late IGF-1 levels.

Relationships between IGF-1 at 35 weeks PMA and (**a**) average parenteral protein intake during first week of life (β −14.47 [−23.97, −4.96] $p = 0.004$), (**b**) day of life full enteral feeds are achieved (β −0.91 [0.91, 1.48] $p = 0.002$), (**c**) IGFBP-3 at 1 week of life (β 19.07 [7.73, 30.41] $p = 0.001$), (**d**) IGFBP-3 at 35 weeks PMA (β 0.02 [0.01, 0.02] $p < 0.001$). Strength of relationship represented by linear regression line. IGF-1: insulin-like growth factor 1, IGFBP-3: insulin-like growth factor binding protein 3, PN: parenteral nutrition, DOL: day of life, PMA: postmenstrual age, Early parenteral protein: g/kg parenteral protein days 2–8 of life.

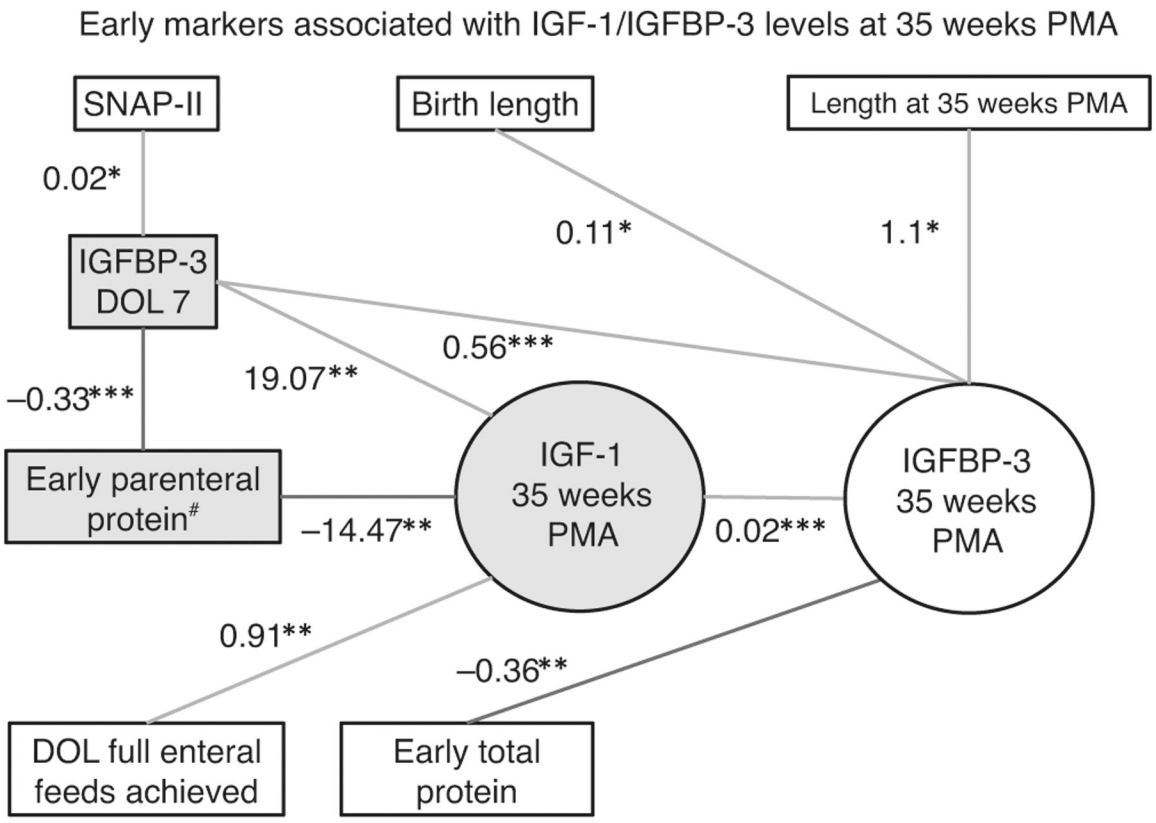

Fig. 3. Early Markers Associated with IGF-1/IGFBP-3 at 35 weeks PMA.

Strength of association represented by β-coefficient. Closed/gray shapes (#): early parenteral protein intake did not significantly mediate the relationship between IGFBP-3 at DOL 7 and IGF-1 at 35 weeks PMA (−4.942, −15.716 to 0.59, $p = 0.20$) measured by Bootstrap test. Green line: positive associations, Red line: negative associations. IGF-1: insulin-like growth factor 1, IGFBP-3: insulin-like growth factor binding protein 3, SNAP-II: Score for Neonatal Acute Physiology, DOL: day of life, PMA: postmenstrual age, Early parenteral protein: g/kg parenteral protein days 2–8 of life. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

Table 1.

Characteristics of patient cohort.

	Variable	*n*	%	Mean	SD
Demographics[*]	Study arm				
	Control	45	52%		
	Intervention	42	48%		
	Sex				
	Female	43	49%		
	Male	44	51%		
	Race				
	White/Caucasian	56	65%		
	Black	9	10%		
	Asian	7	8%		
	More than 1 race identified	2	2%		
	Other/Unknown	13	15%		
	Antenatal Steroids (yes, %)	78	90%		
	Gestational age at birth, wk			27.2	2.5
Hormone Levels	IGF-1 level (ng/mL)				
	DOL 7	75	86%	26.1	9.6
	35 weeks PMA	62	71%	40.2	14.7
	IGFBP-3 level (mcg/mL)				
	DOL 7	77	89%	0.9	0.3
	35 weeks PMA	66	76%	1.3	0.4
Birth weight, length, OFC[*]	Birth weight, grams (z-score)	87		942.9 (−0.2)	285.4 (0.8)
	Birth length, cm (z-score)	87		34.5 (−0.2)	4.2 (1)
	Birth OFC, cm (z-score)	87		24 (−0.5)	3.3 (1.6)
NICU Nutritional Intake[*]	First week of life nutrition	87			
	Kilocalorie intake/kg			95.9	15.8
	Protein intake/kg			4.2	0.4
	Kilocalories/kg from enteral feeds			22.8	18.7

	Variable	*n*	%	Mean	SD
	Protein g/kg from enteral feeds			0.7	0.7
NICU Comorbidities	SNAP-II score, day 1–2	87		25	23.5
	Hyperglycemia >180 mg/dL (# episodes)	87		1.7	2.4
	Insulin treatment (# days)	87		1.1	2.4
	Hypertriglyceridemia >300 mL/dL (# episodes)	87		0.3	0.6
	Hypoglycemia <40 mg/dL (# episodes)	87		0	0.2
	IVH, none/grade 1	73	84%		
	IVH, ≥grade 2	14	16%		

PMA Postmenstrual age, *DOL* Day of life, *SD* Standard deviation, *OFC* Occipital-frontal circumference, *SNAP-II* Score for Neonatal Acute Physiology, *IVH* Intraventricular hemorrhage.

*Portions of this data has been previously published.

Table 2.

Associations between growth, body composition and IGF-1/IGFBP-3 Levels in VLBW Infants.

Measure	Variable	IGF-1 (*n* = 44 DOL 7, *n* = 39 35 wk PMA)			IGFBP-3 (*n* = 45 DOL 7, *n* = 43 35 wk PMA)		
		Time	*β (95% CI)*	*p-value*	*Time*	*β (95% CI)*	*p-value*
Growth	Birth weight, z-score						
		DOL 7	1.99 (−0.92, 4.91)	0.177	DOL 7	0.05 (−0.04, 0.14)	0.272
		35 weeks PMA	0.39 (−4.33, 5.11)	0.869	35 weeks PMA	0.07 (−0.04, 0.19)	0.215
	Birth length, z-score						
		DOL 7	1.42 (−0.85, 3.7)	0.215	DOL 7	0.04 (−0.03, 0.11)	0.230
		35 weeks PMA	2.81 (−0.59, 6.21)	0.103	35 weeks PMA	0.11 (0.02, 0.2)	0.014
	Weight at discharge, z-score						
		DOL 7	0.3 (0, 0.06)	0.086	DOL 7	0.74 (−0.77, 2.25)	0.326
		35 weeks PMA	0.01 (−0.02, 0.03)	0.433	35 weeks PMA	0.75 (−0.13, 1.62)	0.091
	Length at discharge, z-score						
		DOL 7	0.03 (−0.01, 0.06)	0.106	DOL 7	1.41 (−0.16, 2.99)	0.078
		35 weeks PMA	0.01 (−0.01, 0.04)	0.271	35 weeks PMA	1.1 (0.17, 2.03)	0.022
	OFC at discharge, z-score						
		DOL 7	0.02 (−0.01, 0.05)	0.231	DOL 7	0.69 (−0.81, 2.2)	0.358
		35 weeks PMA	0 (−0.03, 0.02)	0.755	35 weeks PMA	−0.02 (−0.96, 0.91)	0.959
Body Composition	Fat mass at discharge, z-score						
		DOL 7	0.07 (0, 0.15)	0.053	DOL 7	0.59 (−2.74, 3.92)	0.722
		35 weeks PMA	0.03 (−0.03, 0.08)	0.329	35 weeks PMA	0.87 (−1, 2.75)	0.352
	Fat free mass at discharge, z-score						
		DOL 7	0.03 (−0.02, 0.07)	0.200	DOL 7	1.44 (−0.45, 3.32)	0.131
		35 weeks PMA	0.01 (−0.02, 0.04)	0.451	35 weeks PMA	1 (−0.07, 2.08)	0.066
	Percent body fat at discharge, %						
		DOL 7	0.03 (−0.04, 0.1)	0.464	DOL 7	0.3 (−2.75, 3.34)	0.844
		35 weeks PMA	0.02 (−0.03, 0.06)	0.494	35 weeks PMA	0.35 (−1.34, 2.04)	0.677
IGF-1/IGFBP-3 Levels	Early IGF-1						
					DOL 7	0.01 (0.01, 0.02)	<0.001

Measure	Variable	IGF-1 (*n* = 44 DOL 7, *n* = 39 35 wk PMA)			IGFBP-3 (*n* = 45 DOL 7, *n* = 43 35 wk PMA)		
		Time	***β (95% CI)***	***p-value***	***Time***	***β (95% CI)***	***p-value***
		35 weeks PMA	0.1 (−0.36, 0.55)	0.676	35 weeks PMA	0.01 (0, 0.02)	0.126
	Early IGFBP-3						
		DOL 7	0.01 (0.01, 0.02)	<0.001			
		35 weeks PMA	19.07 (7.73, 30.41)	0.001	35 weeks PMA	0.56 (0.28, 0.84)	<0.001

All variables were studied separately and adjusted for birth gestational age, PMA at DOL 7/35 weeks, sex, and study arm (intervention vs control).

DOL Day of life, *PMA* Postmenstrual age.