Greater Early Gains in Fat-Free Mass, but Not Fat Mass, Are Associated with Improved Neurodevelopment at 1 Year Corrected Age for Prematurity in Very Low Birth Weight Preterm Infants

Sara E. Ramel, MD[1], Heather L. Gray, MPH[1], Ellen Christiansen, MD[1], Christopher Boys, PhD[1], Michael K. Georgieff, MD[1], and Ellen W. Demerath, PhD[2]

Objective This work investigates the relationship between early body composition changes and neurodevelopment at 1 year age corrected for prematurity (CA).

Study design A prospective, longitudinal study to measure body composition weekly in 34 very low birth weight preterm infants using air displacement plethysmography, beginning when infants stabilized after birth until discharge. Neurodevelopmental testing (Bayley Scales of Infant Development-III) was performed at 12 months CA. Linear mixed effects models were used to obtain inpatient subject-specific changes in fat-free mass (FFM) and fat mass (FM), which were then used as predictors of Bayley subscale scores in subsequent linear regression models, adjusting for potential confounders. Protein and energy provision were calculated for the first week of life.

Results Greater FFM gains while inpatient were associated with improved cognitive and motor scores at 12 months CA ($P = .002$ for both). These relationships remained significant when adjusting for birth weight, gestational age, and intraventricular hemorrhage ($P \leq .05$ for both). Similar analysis was performed for FM gains without significant findings. Increased provision of protein and calories during the first week of life was positively associated with FFM gains ($P \leq .01$ for both), but not FM gains ($P \geq .2$ for both), throughout hospitalization.

Conclusions Increased FFM gains, but not FM gains, during hospitalization are associated with improved neurodevelopment at 12 months CA. As early FM gains may be associated with long-term risk, more research is needed to develop strategies that optimize FFM gains while minimizing FM gains in very low birth weight preterm infants. *(J Pediatr 2016;173:108-15)*.

Very low birth weight (VLBW) preterm infants continue to experience disproportionate growth despite enhanced nutritional practices, with linear growth suppression persisting beyond 18 months of age corrected for prematurity (CA).[1,2] Additionally, these infants have altered body composition when compared with their term counterparts, specifically with lower amounts of fat-free mass (FFM) and increased fat mass (FM) at hospital discharge.[3,4] The impact of this early derangement in growth on metabolic and neurodevelopmental outcomes is just beginning to be understood.

The negative effect of slow weight gain on neurodevelopment is documented in several large studies.[5,6] Additionally, more recent literature has suggested that linear growth, which is often used as a surrogate for FFM gains, is an equally important predictor of later development.[1-2,7] The brain is highly reliant on protein and FFM is a marker of protein accretion; therefore, alterations in body composition likely reflect brain development and processing as well. We have previously reported that increased FFM at term and at 4 months CA is associated with faster brain processing speed at 4 months CA[8]; however, the influence of weekly gains in FM and FFM before term on later and broader assessments of neurodevelopment have not yet been documented. This is important knowledge; earlier growth characteristics, especially before 4 months of age, have been shown to be most beneficial to later neurodevelopment.[1,2,5-7,9]

Enhanced macronutritional regimens provided in the first week of life to VLBW preterm infants have been associated with improved growth and later neurodevelopment.[10] Concerns have also been raised about the long-term metabolic impact of rapid and/or excess catch-up growth owing to excessive provision of calories and protein.[11] Several small studies have documented that enteral supplementation of calories and protein later in the hospitalization are associated with increased FFM

AIC	Akaike Information Criterion
CA	Age corrected for prematurity
DOL	Day of life
FFM	Fat-free mass
FM	Fat mass
IVH	Intraventricular hemorrhage
NICU	Neonatal intensive care unit
SNAP-II	Score for Neonatal Acute Physiology-II
VLBW	Very low birth weight

From the [1]Department of Pediatrics, and [2]Department of Epidemiology and Community Health, University of Minnesota, Minneapolis, MN

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gains, without subsequent increases in FM.[3,12,13] Recently, a larger study of approximately 100 VLBW infants also found that increasing calories and protein throughout hospitalization by implementing a structured nutritional intervention led to improved FFM gains without increasing adiposity or influencing neurodevelopment.[14] The influence of increased provision of macronutrients through parenteral and enteral nutrition specifically during the first week of life on body composition changes, and their relationship to later neurodevelopment, has not yet been documented.

The objective of this study was to establish the relationship between the rate of increase in FM and FFM during hospitalization and neurodevelopment measured at 12 months CA. Additionally, the association between nutritional provision in the first week and gains in FFM and FM throughout hospitalization was explored.

Methods

Fifty-five infants were recruited from the neonatal intensive care unit (NICU) of the University of Minnesota Masonic Children's Hospital from April 2011 to November 2012. Inclusion criteria included birth weight <1500 g and appropriate for gestational age status (between the 3rd and 97th percentile at birth on the Fenton Growth Curve).[15] During the recruitment period, 176 infants weighing <1500 g at birth were admitted to the NICU. Of those excluded or declined, 10 were small for gestational age (<10 percentile), 8 were large for gestational age (>90th percentile), 3 were >1 week old at admission, 6 experienced early clinical instability or died, 47 declined participation, 14 parents were unable to be consented, 17 transferred, 3 had known inability to follow-up after hospitalization, and 3 had reasons unrecorded. The study protocol was approved by the University of Minnesota Institutional Review Board (April 2011). Informed consent was obtained from the parents of the infants.

It was not possible to collect inpatient body composition measurements on 5 infants owing to chronic lung disease requiring continuous respiratory support or transfer to a community hospital at an early gestational age. Of the remaining 55 infants, 34 completed the Bayley Scales of Infant Development-III at 12 months CA. In this paper, only data from the 34 infants with complete data on body composition, nutrition, and neurodevelopment are presented.

Infants were followed daily while they were inpatients by the neonatal nutrition support service. Intake was recorded by the NICU dietician. First week intake was calculated by adding all calories and protein provided either enterally or parenterally from days of life (DOL) 2-8. These dates were chosen because infants were born at different times on the first DOL and therefore the amount of nutrition provided on DOL 1 was variable based on the time of birth.

Cumulative energy deficit was calculated by using a 120 calorie/kg/d goal and subtracting or adding the actual amount of calories received daily. Cumulative protein deficit was calculated by using a 4 g/kg/d goal and subtracting or adding the actual amount of protein received daily. Illness severity on postnatal day 1 was calculated using the Score for Neonatal Acute Physiology-II (SNAP-II), a validated illness severity and mortality risk score for neonates, in which a higher score indicates an increased severity of illness and higher risk of mortality.[16] Data were collected on the number of inpatient days requiring positive pressure, any oxygen therapy, antibiotic use, and steroid use as well as diagnosis of bronchopulmonary dysplasia, necrotizing enterocolitis, retinopathy of prematurity (worst stage), and intraventricular hemorrhage (IVH; most severe grade), because these likely have effects on the outcome variables.[2,3]

Body composition was measured weekly beginning when infants were stable enough to tolerate room air for approximately 5 minutes until discharge using air displacement plethysmography by the PEA POD (COSMED, Ltd, Concord, California). A detailed description of the PEA POD's physical design, operating principles, validation in preterm infants, and measurement procedures have been detailed previously.[17-20] Briefly, the infant's supine length was obtained in duplicate using a standard recumbent length measuring board to the nearest 0.1 cm. Using the integrated electronic scale on the PEA POD, infants were weighed without clothing or diapers to the nearest 0.0001 kg followed by a 2-minute infant body volume measurement in the test chamber. Body density is then computed from body mass and volume. The PEA POD uses a constant FM density (0.9007 g/mL) and known age- and sex-specific FFM density values[21] to calculate amounts of FFM and FM. Head circumference was measured in duplicate using a flexible cloth measuring tape to the nearest 0.1 cm.

Neurodevelopmental testing using the Bayley Scales of Infant Development-III was performed by a pediatric neuropsychologist (C.B.) at 12 months CA in the NICU follow-up clinic.

Statistical Analyses

Statistical analyses were performed using SAS 9.3 (SAS Institute, Cary, North Carolina). Descriptive statistics presented include mean values, SDs, minimum and maximum values for continuous variables, and proportions for categorical variables. Because this study is exploratory, all results are shown; however, correction for multiple testing was performed using the false discovery rate and *P* values that pass the significance threshold indicated.[22]

Linear mixed models were used to obtain inpatient subject-specific rates of change (slopes) and intercept values for FFM, FM, weight, and body fat. The mixed model approach is appropriate when trajectories are fairly uniform across subjects for a number of reasons; linear mixed effect modeling allows for variation in the number of data points per individual and uneven spacing of repeated measurements, allows individuals with only 1 data point to be included (n = 3), and generally reduces measurement error because a best fit line is fitted across all measurements for each subject, rather than relying on incremental changes between individual measurements. Age (or in the case of FM