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Body Composition Changes in Preterm Infants Following Hospital Discharge: Comparison With Term Infants

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Abstract

Background and Objectives: Infants experiencing catch-up growth devote a greater proportion of their energy to fat deposition, potentially at the expense of gains in lean body mass. The objective of the present study was to compare the body composition of preterm and term infants after hospital discharge and to determine the effect of gestational age (GA), birth size, nutrition, and illness on growth in fat-free mass (FFM) after hospitalization.

Patients and Methods: Anthropometric measurements and body composition testing via air displacement plethysmography were performed on 26 appropriate-for-gestational-age (AGA) preterm (mean GA 31.5 ± 2.7 weeks) and 97 AGA term (mean GA 39.8 ± 1.0 weeks) infants at term corrected age (CA) and at 3 to 4 months CA.

Results: At term CA, preterm infants had lower FFM (3.0 vs 3.3 kg, $P < 0.001$), higher percentage of body fat (18.7% vs 15.2%, $P < 0.0001$), lower weight ($P < 0.04$), and shorter length ($P < 0.001$) than term infants. By 3 to 4 months CA, weight, length, percentage of body fat, and FFM were similar in the 2 groups. GA, inpatient nutrition, and illness were associated with FFM at 4 months CA in the preterm infants ($P < 0.05$).

Conclusions: Markedly lower FFM and higher adiposity were observed in preterm infants at term CA, but these differences had lessened and were no longer statistically significant at 3 to 4 months CA. Although early nutrition was associated with growth trajectories in the hospital, the continuing influence of early illness on postdischarge growth suggests that nonnutritional factors (eg, disturbances in the growth hormone axis) also may affect body composition trajectories of preterm infants.

Keywords

body composition; postdischarge growth; premature infant

Preterm infants experience postnatal growth failure that is often still present at discharge and can be associated with long-term neurocognitive outcomes (1–7). Aggressive nutritional

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management of preterm infants has been proposed by the American Association of Pediatrics with the goals of achieving postnatal weight gain that approximate fetal growth rates, achieving fetal body composition, and minimizing later developmental delays (8). Unfortunately, rapid early postnatal weight gain also poses an increased risk for obesity and metabolic syndrome in later life in preterm and small-for-gestational-age (SGA) infants (9–11) and term infants (12,13).

Infancy is generally characterized as a period of rapid fat deposition, with 50% to 60% of energy prioritized to adipose tissue growth (14). Despite their lower body weight and length, preterm infants are characterized by high relative adiposity (percentage of body fat) at hospital discharge compared with term infants (15,16). This body composition difference likely reflects the preferential increase in adipose tissue that is known to occur during catch-up growth (17) and has been observed in preterm (18) as well as SGA infants (19). Possible mechanisms explaining the rapid adipose tissue gains include pancreatic β-cell hyperresponsiveness to glucose (20) and enhanced glucose utilization in adipose tissue (21). Although this adaptive physiology may protect the large, energetically demanding human brain from periodic energy deficits (14), it also may contribute to metabolic risks later in life if continued. Moreover, poor linear growth, a surrogate for fat-free mass (FFM) gains, which accompanies this physiology, may correlate with diminished cognitive outcomes (22).

Although several studies (15,16) have highlighted excess fat accretion in preterm infants, little attention has been paid to the timing and magnitude of recovery of the FFM, a vital piece of information in determining whether there is a critical period that may have a greater effect on neurocognitive development. Furthermore, recent work on postdischarge body composition changes has been conducted largely in non-US settings where nutritional management of preterm infants and the average body habits of the population may differ. The present study aims to define changes in body fat mass and FFM measures from discharge to 4 months' corrected age (CA) in premature infants who have undergone intensive nutritional supplementation, in comparison with healthy term infants, and examine to what extent catch-up growth in fat mass and FFM in preterm infants are influenced by gestational age (GA), size at birth, nutrition, and illness history.

PATIENTS AND METHODS

This was a prospective, observational cohort study on body composition changes in preterm infants between term CA and 4 months' CA. Ethical permission was obtained from the institutional review board at the University of Minnesota. Written consent was obtained from parents.

Twenty-six preterm infants who were admitted to the University of Minnesota Amplatz Children's Hospital between December 2008 and October 2009 were enrolled in the present study before discharge home. One infant was lost to follow-up before the second visit. Inclusion criteria included GA <35 weeks and AGA status at birth (determined by weight between the 10th and 90th percentile on a standardized growth curve (23)). Exclusion criteria included weight <1 kg or >8 kg at discharge and/or inability to lie in a supine position on room air for 5 minutes. Preterm infants were seen at term (38–42 weeks) and at

4 months' CA (55–62 weeks postmenstrual age). Ninety-seven term, singleton, appropriate-for-gestational-age (AGA) infants were recruited as a reference group from an ongoing study on body composition in healthy infants. Term infants of diabetic mothers (gestational diabetes, or preexisting type 1 or 2 diabetes mellitus) and infants with any congenital conditions affecting growth rate were excluded. Term infants were seen at 2 weeks following birth (39–44 weeks) and at 3 to 4 months of age (50–56 weeks postmenstrual age). The difference in mean age at measurement was accounted for in the regression models using postmenstrual age as a covariate for all of the analyses.

Weight, supine length, and head circumference were measured and recorded at 2 outpatient visits. The infant's mass was measured on an electronic scale accurate to the nearest 0.1 g. Supine length was measured on an infant length board (Perspective Enterprises Inc, Portage, MI) to the nearest 0.1 cm. Head circumference was measured using a flexible cloth measuring tape to the nearest 0.1 cm. All of the measurements were performed in duplicate by 1 of the 3 trained researchers (S.E.R., H.L.G., and K.L.O.).

Body composition was assessed using air displacement plethysmography (PEA POD, COSMED USA, Concord, CA) at each visit. A detailed description of the PEA POD's physical design, operating principles, validation, and measurement procedures is provided elsewhere (24–28). A 20-second infant mass measurement using the integrated electronic scale of the PEA POD is 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 the principles of whole body densitometry to derive fat mass and FFM values using body density, fat mass density (0.9007 g/mL) and known age- and sex-specific FFM density values (29).

Descriptive statistics presented include means and standard deviations for continuous variables and proportions for categorical variables. Independent sample *t* tests and χ^2 tests were used to assess significant differences between preterm and term infants. To demonstrate the changes in body composition and growth rates from the first to second visit by term status, general linear models using generalized estimating equations to adjust for the small number of twin pairs in the preterm sample (N = 9) were used to generate least squares mean estimates and standard errors. To account for variation in the exact age at each study visit, the known differences in body composition between sexes, and the effect of feeding type, we included infant's sex, postmenstrual age at each visit, and feeding status (categorized as "exclusively formula-fed" or "partially or exclusively breast-milk-fed") as covariates. Maternal education was also tested as a potential covariate in models comparing term and preterm infants.

Within preterm infants only, the association between various clinical factors (birth weight *z* score, GA, illness score, energy deficit, and protein deficit) and infant growth and body composition outcomes were assessed using partial correlation coefficients after examining scatterplots, which did not indicate nonlinear or threshold effects for any of these bivariate associations. Illness severity was calculated using the Score for Neonatal Acute Physiology system on day 1 of life. This scoring system is a cumulative score of multiple physiological markers of illness in neonates, in which a higher score indicates a greater degree of illness.

The total energy deficit while in the hospital was calculated by subtracting the actual energy received daily from the goal (120 kcal $\cdot$ kg^{-1} $\cdot$ day^{-1}), and the total protein deficit while in the hospital was similarly calculated as the actual grams of protein received was subtracted from the goal (3.5 g $\cdot$ kg^{-1} $\cdot$ day^{-1}). Covariates included were feeding type (breast milk or exclusive formula feeding), infant's sex, and chronological age at the time of visit or the difference in age between visits. All of the tests were performed with SAS 9.2 (SAS Institute Inc, Cary, NC), with statistical significance defined at $P < 0.05$.

RESULTS

Infant characteristics are detailed in Table 1. Infant sex distribution and parental age, race/ethnicity, and weight status were similar between term and preterm infants. There was a difference in maternal education attainment ($P = 0.03$), with fewer mothers of preterm infants achieving greater than a high school education. At visit 1, the percentage of exclusively formula-fed infants was similar in both groups; however, by visit 2, significantly more preterm infants were exclusively formula fed ($P < 0.0001$). Inpatient nutritional data were gathered on only the preterm infants and revealed a total mean inpatient energy deficit of 84.9 kcal/kg and a mean protein deficit of 1.96 g/kg (Table 1).

At term CA, the preterm infants weighed less ($P = 0.04$) and were significantly shorter ($P = 0.001$) (Table 2). Head circumference was similar between the groups. FFM was lower ($P = 0.001$) and fat mass was higher ($P = 0.02$) in the preterm infants, leading to a significantly higher percentage of body fat (18.7% vs 15.2%, $P < 0.0001$) compared with the term cohort. The differences in anthropometrics and body composition between term and preterm infants lessened by 3 to 4 months' CA and were no longer statistically significant except for length z score ($P = 0.03$) (Table 2).

Among preterm infants, GA was positively associated with weight ($P < 0.01$), length ($P < 0.001$), and FFM ($P < 0.01$) at 40 to 42 weeks' postmenstrual age, but only with length and FFM at 4 months' CA ($P < 0.05$) (Table 3). The cumulative hospital protein deficit was negatively associated with weight and FFM at both visits ($P < 0.001$ at visit 1 and $P < 0.05$ at visit 2), whereas hospital energy deficit was negatively associated with FFM at both visits and length at visit 2 ($P < 0.05$ for all). Degree of illness on the first day of life was not associated with any of the measurements at term CA; however, infants with higher illness scores had lower FFM at visit 2 ($P < 0.05$) (Table 3). Birth weight z score also was not associated with differences in measurements taken at term CA, yet it was positively associated with weight, length, fat mass, and percentage of body fat ($P < 0.05$ for all) at visit 2 (Table 3).

Growth between visits was not associated with inpatient nutritional deficits; however, significant associations were noted with GA, illness scores, and weight z score at birth ($P < 0.05$ for all) (Table 3).

DISCUSSION

Previous studies have documented differences in body composition between term and preterm infants, with greater body fat stores at term CA in preterm infants (15,16,30,31).

This is the first study to also define differences and longitudinal changes in FFM in preterm infants from term until 4 months' CA. The diminished FFM gain is important because lean body mass indexes organ growth and development, including the brain (32). Similar to previous reports, the present study found that AGA preterm infants at term postmenstrual age had lower FFM and a higher fat mass than term infants at that age, leading to a higher percentage of body fat (15,30); but in the present study, the relative deficits in FFM and excess fat mass seen in preterm infants at discharge largely returned to levels seen in term infants by 4 months' CA. To our knowledge, this apparent resolution of differences in fat mass and FFM measures has not been documented previously. Further study is needed to evaluate the time course of these changes and the longterm consequences of this rapid catch-up growth in fat mass and FFM change in preterm infants, including long-term body composition and neurodevelopmental outcomes.

The preterm and term infants in our cohort had a much higher average percentage of body fat at term CA than those reported previously by several European groups, despite using the same method of measurement (15,33,34). For example, at term CA, mean percentage of body fat in the preterm infants in the present study was 18.7%, but it was 14.8% in an Italian cohort (15); however, by 4 months' CA, these numbers appear similar (34). This may reflect differences in maternal diet and body habitus (ie, greater maternal BMI in women in the United States), which are known to alter infant body composition at birth, at least in term infants (35,36). This also may reflect international and interhospital variation in nutritional regimens during the infant's initial hospitalization. These potential differences illustrate the need for further study of body composition changes in preterm infants across various populations and under different nutritional regimens.

Although the preterm and term groups appeared similar in growth status and body composition at 3 to 4 months' CA, we noted considerable heterogeneity among the measurements of our preterm infants, which reflects the wide range of GAs (26–34 weeks) at birth in our sample. For this reason, we investigated several possible contributors to variation in growth and body composition within the preterm group. GA was positively associated with FFM at term CA. This is in contrast to findings of Cooke and Griffin (30), who found that FFM was unaffected by GA. Although that study was similar in GA and birth weight to the present one, different methods of body composition assessment and different nutritional regimens may have been used in the 2 settings.

The infants in our study did not follow a prescribed nutritional advancement schedule; however, our unit policy is to start all preterm infants on an amino acid solution containing 2 $g \cdot kg^{-1} \cdot day^{-1}$ of protein immediately at birth and to add protein supplements to achieve 3.5 $g \cdot kg^{-1} \cdot day^{-1}$ of protein once full feeds are established in infants who are born weighing <1500 g. On average, we were able to approach our goal protein intake with a small residual hospital deficit. Despite the small deficit, the inpatient protein deficit was negatively associated with weight, and specifically FFM at both visits; however, it was not associated with postdischarge catch-up growth between visits. Although it has been shown that protein-fortified feedings can increase FFM gains (33), it is unclear whether this can completely correct the diminished lean body mass found in preterm infants upon discharge.

Also, further study is needed into postdischarge protein supplementation and its effects on catch-up growth in lean body mass.

Hospital energy deficit was not associated with weight, but it was associated with the amount of FFM at both visits. Similar to the protein deficit, hospital energy deficit was not associated with catch-up growth postdischarge. Our study findings suggest that early nutritional deficits have lasting effects on body size and specifically lean body mass.

Degree of illness had a negative association with FFM at 4 months' CA, which was not present immediately following hospital discharge. The cause of this latent association is not clear. Illness was also negatively associated with the amount of catch-up growth in length and FFM postdischarge. Although the effects of illness on providing adequate nutrition may play a role, nutritional deficits were not otherwise associated with postdischarge catch-up growth. We speculate that the delayed nature of these effects may be secondary to inflammation or disturbances in the growth hormone/insulin-like growth factor-1 (IGF-1) axis, because critical illness can lead to disturbances in this axis. Both during and after acute stress, patients become relatively growth hormone resistant, with elevated growth hormone levels and inappropriately low IGF-1 levels (37,38). This warrants further study, because IGF-1 and growth hormone have been found to be potentially neuroprotective and neurostimulatory in animal models, as well as in healthy children (39,40), and may suggest a link between lean body mass gains and cognitive development.

We were able to identify several clinical factors that were associated with FFM gains in preterm infants; however, only GA and size at birth were associated with fat mass. We found a positive association between size at birth (weight *z* score) and postdischarge weight gain, specifically in fat mass. This finding was also seen by Cooke and Griffin (30) in a similar population. The finding is not entirely surprising because it is often easier to meet the nutritional, specifically energy, needs of a larger infant. This may also reflect some role of in utero nutrition and growth. Regardless, because of the link between increased postnatal fat gain and the future risk of developing metabolic syndrome and insulin resistance (41–43), these preliminary findings suggest that larger birth weight preterm infants may require different nutritional support than smaller birth weight preterm infants, even within the range of AGA infants. Future studies aimed at optimizing nutrition of the preterm infant should assess effects on both FFM and fat mass and should ideally extend the period of observation beyond discharge from the neonatal intensive care unit because it is clear that significant changes in growth are still occurring until at least 4 months' CA.

The strengths of our study are the use of a reliable and valid method of measuring body composition even in young infants, longitudinal data tracking infants in the critical period after discharge home, and the ability to examine clinical factors (illness score and nutrition) as predictors of the extent of catch-up growth. A potential limitation of our study is that the preterm group included a varied sample, including extremely low birth weight, very low birth weight, and low birth weight infants. This variation also allowed us to examine the effect of GA, birth weight, nutrition, and illness score on the rate of catch-up growth. Future studies with a larger sample size, enabling analysis to be performed on subgroups of preterm infants based on birth weight or GA, may help to better describe the effects of early nutrition and illness and lead to specific interventions that may benefit each group differently. In addition, more detailed outpatient nutritional intake data and markers of inflammation/growth factors would be helpful to identify mechanisms responsible for elevated adiposity during catch-up and to appropriately target future nutritional interventions to achieve optimal health outcomes in preterm infants. Finally, longitudinal tracking both during hospitalization and into the toddler years and beyond will be pertinent to fully understand the timing of these changes and the long-term ramifications of these early differences in body composition.

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TABLE 1.

Infant, maternal, and paternal characteristics by term status

	Preterm (n = 26)	**Term (n = 97)**	***P*[*]**
Infant			
Sex, male, N (%)	16 (61.5)	49 (50.5)	0.32
Gestational age, wk	31.5 (2.7)	39.8 (1.0)	<0.0001
Birth weight, g	1723.6 (586.5)	3539.2 (447.4)	<0.0001
Birth weight *z* score	−0.03 (0.60)	0.49 (0.91)	0.0009
Energy deficit, kcal/kg[†]	84.90 (51.50)[§]	—	—
Protein deficit, g/kg[‡]	1.96 (2.12)[‖]	—	—
Score for neonatal acute physiology	8.88 (6.74)[¶]	—	—
Maternal and paternal			
Maternal age, y	30.6 (4.8)	31.1 (4.8)	0.61
Paternal age, y	32.4 (4.6)	33.0 (5.8)	0.66
Maternal race, white, N (%)	23 (88.5)	80 (82.5)	0.46
Paternal race, white, N (%)	20 (76.9)	77 (79.4)	0.79
Maternal education, N >high school (%)	17 (65.4)	82 (84.5)	0.03
Paternal education, N >high school (%)	18 (69.2)	73 (76.0)	0.48
Maternal weight, prepregnancy, kg	74.1 (20.3)	70.6 (16.8)	0.37
Maternal weight gain, kg	14.2 (6.4)	15.3 (5.8)	0.40
Maternal BMI, kg/m^2	26.9 (7.9)	25.9 (6.5)	0.49
Paternal BMI, kg/m^2	26.4 (3.7)	27.5 (5.5)	0.28
Feeding type			
Exclusively formula fed at visit 1, n (%)	5 (19.2)	11 (11.3)	0.29
Exclusively formula fed at visit 2, n (%)	18 (69.2)	24 (30.8)	<0.0001

Data expressed as mean (standard deviation) for continuous variables or n (%) for categorical variables. BMI = body mass index.

[*] Student *t* tests used to compare continuous variables and χ^2 or Fisher exact test used to compare categorical variables.

[†] Energy deficit calculated by using a 120 kcal · kg^{-1} · day^{-1} goal and subtracting or adding the actual amount of energy received.

[‡] Protein deficit calculated by using a goal of 3.5 g · kg^{-1} · day^{-1} and subtracting or adding the actual amount of grams received.

[§] Values ranged from 17.83 to 230.56.

[∥] Values ranged from −2.59 to 5.93.

[¶] Values ranged from 2 to 35.

TABLE 2.

Measurements at term corrected age and 3 to 4 months' corrected age in 26 appropriate-for-gestational-age preterm and 97 appropriate-for-gestational-age term infants

	Visit 1 (40–42 wk)			Visit 2 (53–58 wk)		
	Preterm (n = 26)	**Term (n = 97)**	***P***	**Preterm (n = 26)**	**Term (n = 97)**	***P***
Weight, kg[*]	3.65 (0.11)	3.88 (0.06)	0.04	6.41 (0.28)	6.18 (0.09)	0.5
Length, cm[*]	51.17 (0.46)	52.74 (0.25)	0.001	61.24 (0.84)	61.74 (0.28)	0.6
Weight *z* score[†]	0.02 (0.20)	0.22 (0.12)	0.3	−0.49 (0.23)	−0.04 (0.11)	0.09
Length *z* score[†]	−0.19 (0.24)	0.30 (0.15)	0.06	−0.30 (0.22)	0.25 (0.10)	0.03
Head circumference, cm[*]	36.79 (0.23)	36.74 (0.17)	0.8	41.51 (0.35)	41.26 (0.16)	0.6
FFM, kg[*]	2.97 (0.10)	3.29 (0.05)	0.001	4.60 (0.16)	4.69 (0.06)	0.7
Fat mass, kg[*]	0.68 (0.03)	0.59 (0.02)	0.02	1.81 (0.17)	1.49 (0.06)	0.1
Body fat, %[*]	18.69 (0.79)	15.15 (0.46)	<0.0001	27.74 (1.74)	23.90 (0.65)	0.07

Data expressed as least squares means (standard error). FFM = fat-free mass.

[*] Adjusted for infant's sex, feeding type, and postmenstrual days at time of measurement.

[†] Adjusted for feeding type.

TABLE 3.

Association of gestational age, initial illness, size at birth, and inpatient nutrition with anthropometries and body composition following hospital discharge in 26 preterm infants

	Weight	Length	FFM	Fat mass	Body fat, %
Visit 1					
GA[a]	0.5931**	0.6434***	0.6036**	0.2917	−0.0199
SNAP[b]	−0.0177	−0.1069	−0.1755	0.3229	0.3826
WAZ[a]	0.3421	0.3573	0.2906	0.3131	0.1891
kcal[b]	−0.3973	−0.1715	−0.5118**	0.0529	0.3440
Protein[b]	−0.6928***	−0.2064	−0.7310***	−0.2469	0.1277
Visit 2					
GA[a]	0.2539	0.4643*	0.4975*	−0.1558	−0.3635
SNAP[b]	−0.1976	−0.3437	−0.5173*	0.2080	0.3917
WAZ[a]	0.5162*	0.4203*	0.2739	0.5596**	0.4361*
kcal[b]	−0.3648	−0.5097*	−0.5101*	−0.0803	0.0733
Protein[b]	−0.4228*	−0.2572	−0.4879*	−0.2008	−0.0663
Change (visit 1 to visit 2)					
GA[c]	0.2885	−0.4389*	−0.1263	0.4704*	0.5463**
SNAP[d]	−0.2067	−0.4415*	−0.5041*	0.1325	0.1208
WAZ[c]	0.4679*	0.3989	0.1299	0.5121*	0.3589
kcal[d]	−0.1447	−0.0774	−0.0764	−0.1401	−0.2753
Protein[d]	−0.1820	−0.0261	0.0173	−0.2718	−0.3257

FFM = fat-free mass; GA = gestational age; kcal = energy deficit; protein = protein deficit; SNAP = Score for Neonatal Acute Physiology; WAZ = birth weight *z* score.

[a] Adjusted for infant’s sex, feeding type, and chronological age at visit.

[b] Adjusted for infant’s sex, feeding type, chronological age at visit, and gestational age.

[c] Adjusted for infant’s sex, feeding type, and difference in age from visit 1 to visit 2.

[d] Adjusted for infant’s sex, feeding type, difference in age from visit 1 to visit 2, and gestational age.

[*] $P < 0.05$;

[**] $P < 0.01$;

[***] $P < 0.001$.