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Body Composition and Its Components in Preterm and Term Newborns: A Cross-Sectional, Multi-Modal Investigation

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Abstract

Objective—A prospective, cross-sectional, observational study in pre- and term infants was performed to compare multimodal measurements of body composition namely, limb ultrasound, bone quantitative ultrasound and dual X-ray absorptiometry (DXA).

Patients and Methods—102 preterm and term appropriate for gestational age infants were enrolled from the newborn nursery and neonatal intensive care unit. Infants were included when they were medically stable, in an open crib, on full enteral feeds and within one week of anticipated discharge. Correlations among the various measurements of body composition were performed using standard techniques. A comparison between preterm infant (born at 28-32w) reaching term to term born infants was performed.

Results and Conclusions—Limb ultrasound estimates of cross sectional areas of lean and fat tissue in a region of tissue (i.e., the leg) were remarkably correlated with regional and whole body estimates of fat free mass and fat obtained from DXA suggesting the potential usefulness of muscle ultrasound as an investigative tool for studying aspects of body composition in this fragile population. There was a weak but significant correlation between quantitative ultrasound measurements of bone strength and DXA derived BMD. Preterm infants reaching term had significantly lower body weight, length, head circumference, muscle and fat cross sectional area, bone SOS, whole body and regional lean body mass, fat mass and BMD compared to term born infants. Current post-natal care and nutritional support in preterm infants is still unable to match the in-utero environment for optimal growth and bone development. The use of relatively simple bedside, non invasive body composition measurements may assist in the understanding how changes in different components of body composition early in life affect later growth and development.

Keywords

bone mineral density; fat; muscle; ultrasound; infants; prematurity

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Introduction

In healthy newborns, lean (predominately muscle), fat, and bone tissues, the key components of body mass, increase rapidly. The pattern of this increase is profoundly altered by premature birth, and disruptions in the ontogeny [or as suggested by Wells et al. (1), "programming"] of body composition are associated with seemingly disparate lifelong conditions such as obesity and increased risk of cardiovascular disease (2;3) on the one hand and growth retardation (4) and bone disease of prematurity (5) on the other. Although little is known about the mechanisms that control the early-in-life development of muscle, fat, and bone, there is mounting evidence that the factors regulating body composition among these compartments are distinct leading to differing rates of growth. In the case of muscle and fat tissues, for example, growth may be antagonistic (6): Shibata and coworkers (7) recently noted in fetal animal models that muscle-derived myostatin may play a role in intramuscular fat by decreasing myogenesis and increasing adipogenesis. In contrast, in the case of muscle and bone, growth of the two tissues may be synergistic (8).

Body composition is difficult to study in premature babies largely because of the limited tools appropriate for this fragile population. We used a multimodal approach simultaneously employing three distinct techniques previously used in premature babies, albeit in relatively small samples: 1) dual X-ray absorptiometry (DXA) which measures lean, fat, and bone tissue and can be used for these measurements both for the whole organism and for specific anatomic regions; 2) limb ultrasound (LUS) which quantifies regional muscle and fat mass (9;10); and 3) quantitative bone ultrasonography (QUS) which is related to bone strength (11;12).

We chose a cross-sectional approach specifically so that we could readily compare results obtained from the three different methods of assessing body composition components over a wide range of body masses. This approach would help determine the feasibility of these measurements "at the bedside". Finally, the study would, we believe, begin to demonstrate how these techniques could be optimally used to assess the development of body composition in newborns in longitudinal studies.

We also wanted to study the differences in body composition measurements in premature infants versus term infants at the time they approach discharge in order to understand the impact of premature birth and neonatal intensive care unit (NICU) stay on infant growth. We hypothesized that 1) regional muscle, fat and bone measurements obtained by ultrasound at the bedside would correlate with simultaneously obtained whole body DXA measurements of body composition; and 2) body composition in premature infants approaching time of discharge would be different from newborn infants of similar post menstrual age.

Participants and Methods

Participants

A total of 102 appropriate for gestational age, preterm and term infants (Table 1) hospitalized in the neonatal intensive care unit or newborn nursery at UC Irvine Medical Center were enrolled in this study. Infants were recruited when they were medically stable, in an open crib, on full enteral feeds, and approaching discharge. The infants were averaging over 120 – 130 Kcals/kg/day and demonstrated progressive weight gain. Exclusion criteria included infants with evidence of chromosomal or other major genetic abnormality, suspected neuromuscular disorders and significant chronic lung disease. Infants born to mothers with diabetes, substance abuse and other endocrine abnormalities were also excluded. The study was approved by the UC Irvine Institutional Review Board (IRB) and written parental consent was obtained from both parents in accordance with IRB

requirements. All measurements where performed prior to discharge from the NICU or newborn nursery. The post menstrual age (PMA) of the infants at the time of the measurement was calculated from the mother's last menstrual period.

Weight, length and head circumference

Standard electronic calibrated scales were used to measure weight. Length was measured on a standard length measuring board by two trained NICU nurses. Head circumference was measured by a disposable paper measuring tape. All measurements were obtained on the day of Ultrasound and DXA measurements.

DXA

All participating infants were transported in a standard neonatal transport incubator to the DXA site located in the same building floor as the NICU. Hologic QDR Discovery-A (Hologic Inc, Bedford MA) machine was used for DXA measurements. The infants were swaddled in a cotton sheet and a pacifier with sucrose was used to minimize movement artifacts. A heat lamp was used to maintain a comfortable body temperature. Pediatric software in the DXA scanner was used to analyze whole body and regional (right tibia) bone area, bone mineral content and bone mineral density. Apparent bone mineral density was calculated by dividing the BMD to body length (m).

Limb Ultrasound

Clear visualization of muscle boundaries is possible since epimysium surrounding the muscles is highly reflective. Limb ultrasound has been used to assess muscle mass (muscular hypertrophy) in an infant with myostatin deficiency (13), and it has also been used to assess cardiac and skeletal muscle mass in small animals (14;15). Besides measurement of muscle mass, fat mass can also be estimated with this technique (16). All studies were performed by a trained single ultrasonographer from the UC Irvine Department of Radiology using a Philips ATL machine (model) with 12 MHz probe. Scans were obtained of right calf, one-third the distance from the poplitial fossa to the heel. Images were stored digitally as bitmap files. Total leg cross sectional area and muscle cross sectional area (inclusive of tibia and fibula) on these ultrasound scans were measured using Scion software (obtained from the NIH web site, http://rsb.info.nih.gov/nih-image/about.html). The difference between the two was recorded as subcutaneous fat cross sectional area.

Quantitative Bone Ultrasound

Speed of Sound (SOS) measurements were made using the Sunlight Premiere Quantitative Bone Ultrasound (QUS) machine by a trained study team nurse. A standardized procedure was followed and the probe was placed on the left tibia at ½ the measured distance between the apex of the heel and the distal patellar apex. After calibrating the machine with a standard phantom, three measurements were obtained from the same site and the mean value was calculated.

All technicians performing either DXA, limb or bone US, were blinded to the prior medical history of the examined infants.

Statistical analysis

Data are presented descriptively with mean and 95% confidence interval (CI) and frequency and percentage. Pearson's product-moment correlations were used to describe the relationships between different measurements. Since all the measurements are also correlated with age, Pearson's partial correlations were also obtained to adjust for the effect of PMA.

A linear model was also fitted for ultrasound and DXA measured lean mass, fat mass and bone measurements with PMA as a predictor. All measurements were standardized so the slopes against age could be compatible. The mean standardized slope and 95% CI against PMA and gestational age are presented separately with bar chart.

Results

Sample Population

Descriptive data of the infants enrolled in the study are shown in Table 1. The mean gestational age at birth for the group was 33.7 ±0.5 weeks. Sixty-three infants were born premature (gestational age 30.3±0.3) and 39 were born at term (>37 weeks gestation, gestational age 39.4±0.2). Due to heterogeneity of the participants, infant were divided into four groups according to their gestational age [term >37w (n=39), and preterm: 23-28w (n=20), 29-32w (n=26) and 33-36w (n=17)]. By group birth characteristics, physical measurements and body composition (DXA and US), are presented in table 2. No gender differences were found in all measurements. DXA measurements of bone and muscle were obtained in all infants. Due to incomplete visualization of muscle or subcutaneous fat on MUS, cross sectional muscle area measurements were made in 100 infant (98%) and fat area measurements were obtained in 92 infants (90%). At discharge, only the group of 23-28w premature infants reached PMA of term, therefore we only compared this age group to the results of the infants born at term. Body weight, length, head circumference, muscle and fat cross sectional area, bone SOS, whole body and regional lean body mass, fat mass and BMD were significantly lower in the preterm infants reaching term. No significant difference was found in percent body fat and in the ratio of lean mass (LM) to fat mass (FM). Interestingly, fat percentage in the most preterm infants (23-28w) reaching term was significantly greater then in both other preterm groups (29-32 and 33-36w).

Correlations of Bone Measurements

Whole body bone mineral density was highly correlated with total body lean tissue (Figure 1). Bone SOS had weak but significant correlation with BMD (r=0.48 for whole body and r=0.45 for regional DXA) (Figure 2). After adjusting for PMA, these correlations slightly improved (r=0.56 and r=0.49 for whole body and regional DXA, respectively).

Correlations among Measurements of Lean/Muscle, Fat, and Body Weight

There was a very strong correlation (r=0.99) between DEXA total mass and measured weight. There were substantial correlations between muscle cross sectional area determined by limb ultrasound with DXA-derived whole body (r=0.82) and regional lean mass (r=0.71) (Figure 3). After adjusting to PMA, the correlations between limb ultrasound muscle cross section and DXA-derived lean mass decreased [(r=0.63) for whole body and (r=0. 51) for regional lean mass].

There were also strong correlations between fat cross sectional area by limb ultrasound and fat mass measured by both whole body DXA (r=0.82) and regional DXA (r=0.81) (Figure 4). After adjusting to PMA, the correlations slightly decreased [whole body DXA (r=0.67) and regional DXA (r=0.67)].

Mean slopes and 95% CI for measurements of body composition adjusted for PMA in the linear regression model are presented in Figure 5. All slopes were significantly different from zero.

Discussion

The aim of the present study was to examine the feasibility of non-invasive bedside ultrasound measurement of body composition in infants, compared to DXA measurements. We found significant correlations between limb ultrasound measurements of muscle and fat, with regional and whole body DXA. These correlations remained significant when adjusted to PMA. Weaker correlations were found between bone strength, measured by bone QUS, and BMD, BMC and apparent BMD by DEXA. Our data support the idea that relatively simple bedside measurements could be used to assess body composition in this fragile population.

Consistent with our second hypothesis, we found that preterm infants reaching term had significantly lower body weight, length, head circumference, muscle and fat cross sectional area, bone SOS, whole body and regional lean body mass, fat mass and BMD compared to term born infants. These results demonstrate that the optimal care in the NICU (advancement of treatment and nutritional support) is still unable to equal intrauterine conditions.

DXA is now widely accepted as a reliable and accurate measure of body composition in infants (17). In the past, the accuracy of DXA in small animals and human infants, was questioned. In poorly mineralized bone, BMC may be underestimated (18), and in small subjects, fat mass may be overestimated (19). However, with correctional equations (19) and the development of the faster fan beam scans, such as used in the present study, DXA was found to be valid, reliable and accurate in small animals. Reference data for preterm and term infants have been reported previously (19;20). In the present study, total mass measured by DXA is highly correlated with measured weight (r=0.99). Our DXA measurements of LM and FM are remarkably similar to chemical analysis of stillborns (21), to body composition measurements using total body water and total body potassium (22) and are also consistent with reference values for term newborns (23). Our DXA body composition, BMD and BMC measurements in preterm infants (28-32 weeks) are comparable to similar gestational age infants studied at discharge (24). Previous studies reported higher fat mass percentage for term infants and preterm infants approaching term, ranging from 15-21% (17). Those relatively high fat percentages were reported using older versions of DXA machines and software, and are now believed to be an overestimation corrected by using appropriate equations in the newer DXA machines. Percentage of body fat in term infants was also similar to previously reported chemical analysis values (25).

A positive correlation was found between lean mass and whole body bone mineral density. There is mounting evidence to support the concept of the functional “bone-muscle unit” in which muscle activity can stimulate bone growth through mechanoreceptors (26) and through the activity of hormones like IGF-I which influence both muscle and bone (27). Indeed, absent or poor fetal movement is associated with impaired bone mineralization (28;29). More recently, in fetal Myod-Myf5 deficient mice--congenitally lacking striated muscle and having no functioning “bone-muscle unit” or in utero mechanical loading through muscle activity, Gomez et al. (30) found that bone was profoundly abnormal and poorly mineralized.

DXA measures BMD from the absorption of x-rays, the latter is correlated with the degree of bone mineralization. Quantitative ultrasound is used to derive an index of “bone strength” based on the speed of a sound wave propagation through the heterogeneous bone tissue. The technique has been shown to correlate with BMD measured by DXA in adults (31;32), but there are conflicting reports in the pediatric population (33) (34). Although QUS has been used to study bone strength in premature babies (35), there are few, if any studies, in which

the two modalities were used simultaneously in premature babies. We found modest but significant correlations between bone quantitative ultrasound and both total body and regional DXA derived BMD (Figure 2). Clearly, the two modalities are measuring somewhat different but related properties of bone in the newborn. While DXA measures *quantitative* aspects of bone mineral density, bone QUS is also influenced by *qualitative* factors that contribute to bone strength such as bone elasticity, microarchitecture and fatigue damage (36). Thus, although the two modalities are not interchangeable, a complementary use of both methods may better reflect "true" bone strength. Both bone strength and BMD by DXA were found to be significantly lower in the preterm infants, even in those reaching term. It is not known yet whether this osteopenia of prematurity is a self-resolving condition or a disease with long term consequences. Chan et al. recently demonstrated reduced bone mineralization in 7 years old children who were born prematurely (37). Even if bone mineralization improves spontaneously, the prolonged period of demineralization in early childhood may lead to overt rickets, bone fractures, and potentially reduce peak bone mass.

Most remarkable was the observation of the substantial correlation between the measure of muscle and fat CSA in a single limb by ultrasound with DXA derived measurements of lean and fat tissues both at the regional and whole body level (Figures 3 and 4). While reference values of muscle size using ultrasound are available for the adult population, normative data for the premature infant are scarce and mostly focuses on muscle thickness rather than cross-sectional area or volume (38;39). In a sub group of infants (data not shown) we obtained ultrasound measurements of the calf and measured muscle depth from the epimysium to the tibia similar to the technique described by Scholten. We found no significant correlation between muscle thickness and DXA lean mass. In contrast, our data indicate that cross sectional areas of the muscle and subcutaneous fat in a single limb obtained by ultrasound were highly correlated with DXA measurements of lean and fat tissue both regionally and for the total body. On a technical note, we found that it is important for these measurements to be obtained at precise locations with consistent technique to obtain valid results.

Using all three techniques, we studied the body composition of preterm infants approaching time of discharge. For this purpose we used the post menstrual age to compare appropriate for gestational age infants of different degrees of maturity. Only the most premature group (born at 23-28 weeks) had PMA equivalent to term at the time of the measurements. We found that this group of preterm infants reaching term had significantly lower body weight, length, head circumference, muscle and fat cross sectional area, bone SOS, whole body and regional lean body mass, fat mass and BMD compared to term born infants. However, similar to previous observation (40), these infants maintained LM to FM proportions similar to term infants. Interestingly, in the two other preterm groups (born at 28-32 and 33-36w), who were discharged earlier from the NICU, and did not reach term, fat percentage was lower and the thus the ratio of LM to FM was higher. This is consistent with the fact that during fetal life premature infants appear to follow a similar pattern with an earlier accretion of LM followed by accumulation of fat mass. Therefore, preterm infants who did not reach term gained mainly LM, while those reaching term before discharge gained both LM and FM.

The relationship between the magnitude and rate of change of the fat mass early in life with conditions such as obesity and its accompanying insulin resistance and increased cardiovascular disease risk in adolescence and adulthood has spurred renewed interest into the mechanisms that control fat accretion in the fetus and newborn, in particular, on the hormones and mediators that constitute the "fat-brain axis" even in fetuses (41). A disproportionately higher rate in the recovery of body fat compared to lean tissue in preterm infants during early post-natal life (i.e. preferential 'catch-up fat'), as recently suggested by

Dulloo et al. may be a central event in growth trajectories to obesity and to diseases that cluster into the insulin resistance (metabolic) syndrome (42) seen in this population (43).

Conclusion

In summary, the results of this cross-sectional multimodal analysis suggest the potential usefulness of muscle ultrasound as an investigative tool for studying aspects of body composition in this fragile population. There was also a weak but significant correlation between quantitative ultrasound measurements of bone strength and DXA derived BMD, but, when applied to investigating the rate of bone mineralization, the techniques proved not to be interchangeable. Current post-natal care and nutritional support in preterm infants is still unable to match the in-utero environment for optimal growth and bone development. Understanding how different components of body composition change early in life may shed light on the mechanisms that link these early changes in fat, muscle, and bone tissue with obesity and osteopenia that occur in later periods of growth and development.

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Abbreviations

DXA	dual X-ray absorptiometry
IGF-I	insulin-like growth factor-I

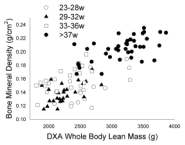

Figure 1.

Bone mineral density as a function of DXA derived measurements of whole body lean tissue by group. BMD was significantly correlated to lean tissue (r=0.80).

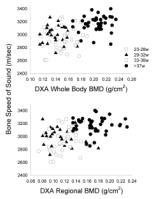

Figure 2.

Comparison of bone quantitative ultrasound with bone mineral density measured by DXA for the whole body (upper panel) and regional (lower panel) by group. There were modest but significant correlations between the two modalities for both (whole body, r=0.48; regional, r=0.45).

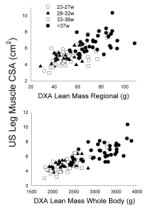

Figure 3.
US Leg muscle CSA as a function of DXA measured regional (leg) lean mass (UPPER PANEL) and whole body lean mass (LOWER PANEL) by group. In both cases, the US measurement in a single leg was highly correlated with the DXA results (for regional lean mass, r=0.72; for whole body lean mass, r=0.81).

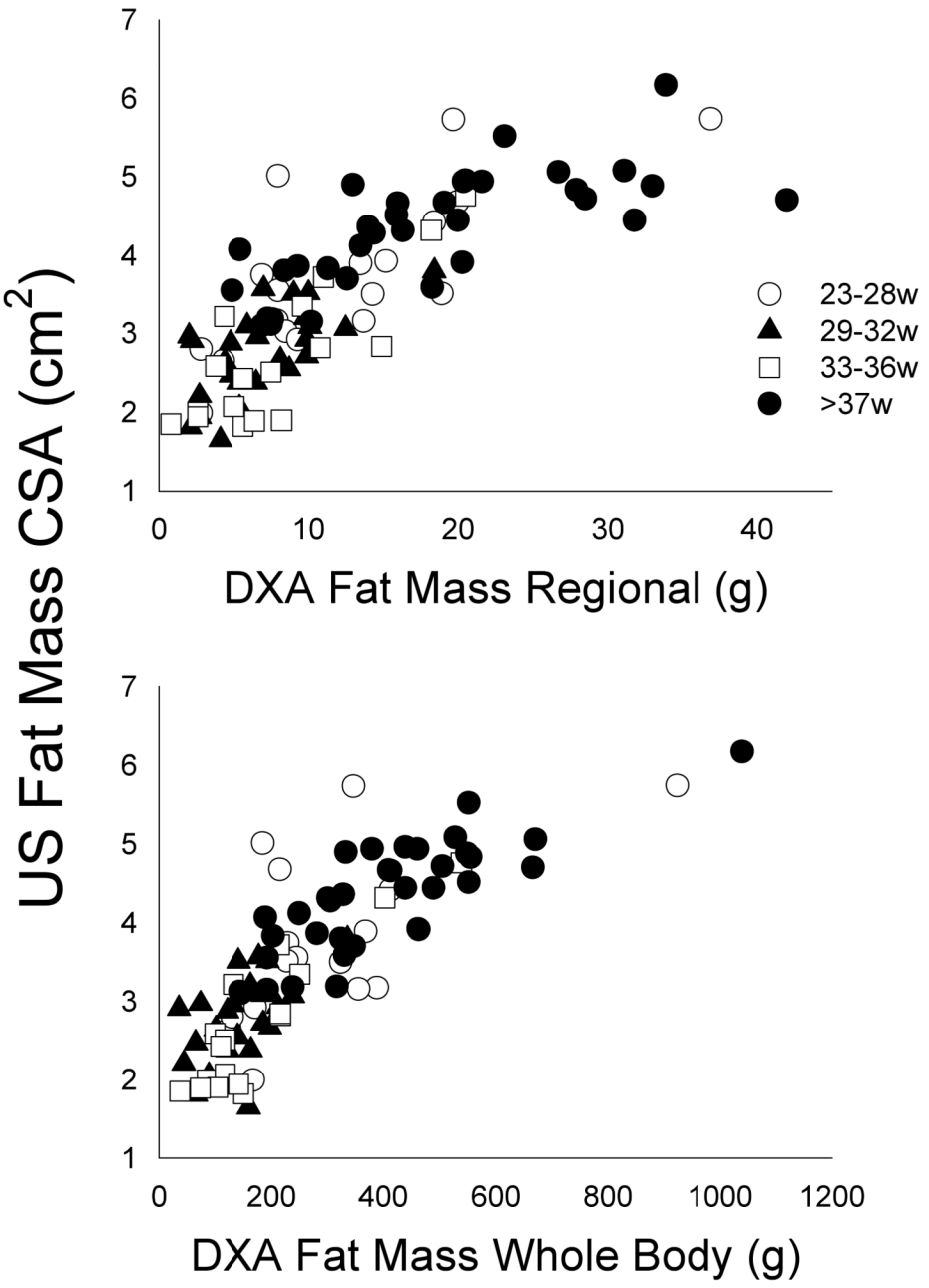

Figure 4.
US determined Leg fat CSA as a function of DXA measured regional (leg) fat mass (UPPER PANEL) and whole body fat mass (LOWER PANEL) by group. In both cases, the US measurement in a single leg was highly correlated with the DXA results (for leg fat mass, r=0.81; for whole body fat mass, r=0.82).

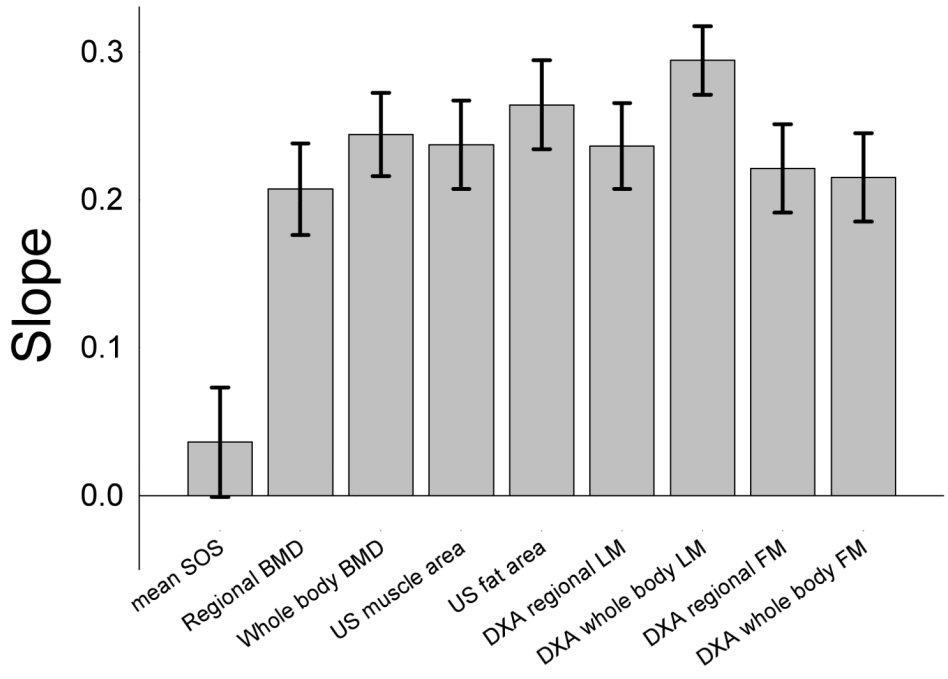

Figure 5.
Mean slopes and 95% CI adjusted for PMA in the linear regression model of ultrasound and DXA measurements of Bone SOS, regional BMD, whole body BMD, muscle and fat CSA, regional and whole body lean mass (LM) by DXA, regional and whole body fat mass (FM) by DXA. All slopes except for bone SOS were significantly different from zero.

Table 1

Participant Characteristics (N=102).

	Mean	**95% CI**
Gestational age at birth (weeks)	33.7	(32.6,34.7)
Chronological age (days)	28.5	(21.7,35.2)
Post menstrual age (weeks)	37.8	(37.3,38.4)
Birth weight (g)	2296.0	(2076.1,2516.0)
Birth length (cm)	44.2	(42.9,45.5)
Birth head circumference (cm)	30.7	(29.8,31.5)
	Frequency	Percentage
Male	51	50.0
Hispanic	49	48.0
Caucasian	35	34.3
African American	8	7.8
Asian	8	7.8
Others	2	2.0

Table 2

By group Participant Characteristics

	23-28 weeks (n=20)	29-32 weeks (n=26)	33-36 weeks (n=17)	37-42 weeks (n=39)
Gestational age (weeks)	25.9 (25.1,26.6)	30.8 (30.4,31.3)	34.2 (33.6,34.7)	39.4 (39.0,39.8)
Chronological age (days)	89.3 (77.7,100.8)	31.2 (27.4,34.9)	9.6 (6.3,12.9)	3.8 (2.1,5.4)
Post menstrual age (weeks)	38.6 (37.2,40.0)	35.3 (34.9,35.7)	35.6 (35.0,36.2)	40.1 (39.7,40.5)
Birth weight (g)	864.8 (738.2,991.3)	1609.2 (1498.1,1720.3)	2225.0 (2015.0,2435.0)	3518.9 (3360.5,3677.2)
Birth length (cm)	34.0 (32.1,36.0)	41.6 (40.5,42.7)	45.2 (44.2,46.2)	50.7 (50.0,51.4)
Birth head circumference (cm)	24.1 (22.5,25.7)	29.0 (28.3,29.7)	31.4 (30.6,32.2)	34.8 (34.3,35.3)
Physical measurements				
Weight (g)	2679.4* (2428.8,2929.9)	2215.5 (2096.5,2334.5)	2256.4 (2060.1,2452.6)	3453.3 (3296.5,3610.0)
Length (cm)	46.0* (44.6,47.4)	45.1 (44.3,45.9)	45.7 (44.6,46.8)	50.5 (49.7,51.2)
HC (cm)	33.4* (32.6,34.1)	32.1 (31.5,32.6)	31.9 (31.2,32.7)	35.1 (34.6,35.7)
Ultrasound measurements				
Muscle area (cm^2)	5.4* (4.9,5.9)	4.8 (4.6,5.1)	2.7 (2.2,3.2)	6.6 (6.2,7.0)
Fat area (cm^2)	3.7* (3.2,4.3)	2.8 (2.5,3)	3068.0 (2997.3,3138.6)	4.3 (4.1,4.6)
Bone SOS (m/s)	2797.4* (2720.4,2874.4)	3003.9 (2949.8,3058)	2470.3 (2267.2,2673.4)	3168.4 (3129.0,3207.9)
DEXA measurements -- Whole body				
Lean mass (g)	2556.9* (2374.2,2739.6)	2251.0 (2152.8,2349.1)	2250.4 (2098.7,2402.1)	3162.8 (3033.7,3291.8)
Fat mass (g)	345.6* (240.3,450.9)	142.0 (114.9,169.1)	177.3 (112.1,242.5)	417.6 (357,478.2)
BMD (g/cm^3)	0.145* (0.135,0.154)	0.139 (0.133,0.145)	0.161 (0.152,0.170)	0.204 (0.199,0.210)
Apparent BMD	0.314* (0.298,0.330)	0.308 (0.297,0.320)	0.352 (0.339,0.367)	0.405 (0.396,0.414)
BMC (g/cm)	43.0* (37.2,48.8)	35.3 (32.7,38.0)	42.6 (37.6,47.6)	72.5 (68.3,76.7)
% fat	11.1 (8.8,13.5)	5.7 (4.8,6.6)	6.8 (4.8,8.7)	11.2 (9.9,12.5)
DEXA measurements – Regional				
Lean mass (g)	52.2* (45.7,58.7)	47.1 (43.7,50.5)	52.2 (45.3,59)	74.4 (70.3,78.4)
Fat mass (g)	13.9* (9.6,18.2)	6.9 (5.4,8.4)	8.1 (5.2,10.9)	19.0 (16.0,22.0)

	23-28 weeks (n=20)	29-32 weeks (n=26)	33-36 weeks (n=17)	37-42 weeks (n=39)
BMD (g/cm^3)	0.106* (0.098,0.115)	0.113 (0.103,0.123)	0.128 (0.119,0.138)	0.172 (0.164,0.180)
Apparent BMD	0.231* (0.216,0.246)	0.249 (0.230,0.269)	0.280 (0.262,0.299)	0.340 (0.325,0.355)
BMC (g/cm)	1.2* (1.0,1.4)	1.2 (1.0,1.3)	1.5 (1.3,1.7)	2.7 (2.5,2.8)
% fat	19.0 (15.7,22.4)	12.1 (10.0,14.3)	12.1 (9.1,15.1)	19.2 (16.8,21.7)

*Significant difference between term born and preterm infants born at 28-32 weeks reaching term.