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Association between supraclavicular brown adipose tissue composition at birth and adiposity gain from birth to 6 months of age

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BACKGROUND: Brown adipose tissue (BAT) is associated with higher energy expenditure and lower adiposity in adults. However, the relationship between BAT composition and adiposity in early life is unknown. The objective of this study was to test the hypothesis that brown fat composition at birth is prospectively associated with adiposity gain during the first 6 months of postnatal life.

METHODS: $N = 35$ healthy infants were followed up prospectively from intrauterine life and birth through 6 months of age. Dixon magnetic resonance imaging (MRI) scans were conducted during the neonatal period to characterize supraclavicular BAT composition. Dual-energy X-ray absorptiometry to assess total body composition was performed within the first and sixth months of life.

RESULTS: After adjusting for potential confounding factors, a more brown-like composition (smaller fat fraction) of the supraclavicular BAT depot was associated with a smaller increase in percent body fat over the first 6 months of postnatal life.

CONCLUSIONS: A more brown-like BAT composition at birth appears to be protective against excess adiposity gain in early life. Newborn BAT tissue may constitute a target for prevention strategies against the subsequent development of obesity.

The severity and magnitude of health and other problems conferred by obesity/adiposity and metabolic dysfunction is well recognized (1). It is also well established that, once an individual becomes obese, it is difficult to lose weight, and even more difficult to sustain weight loss (2,3). For these reasons, it is important to gain a better understanding of the early/developmental origins of individual differences in the propensity for weight and fat mass gain, in order to predict obesity (or, more precisely, excess adiposity) risk, and to develop strategies for primary prevention before an individual becomes overweight or obese, or secondary interventions to increase the likelihood of a more sustained response to weight-loss strategies (3,4).

At the individual level, obesity results when energy intake exceeds energy expenditure. Thus, any effective treatment for obesity must alter total energy balance by either decreasing energy intake and/or increasing energy expenditure. In contrast to white adipose tissue (WAT), which functions to store fat, brown adipose tissue (BAT) is a specialized tissue that expends energy via lipid metabolism and thermogenesis pathways, facilitated by its uncoupling protein UCP-1 (ref. 5). The presence of substantial depots of BAT in newborns and its crucial, life-preserving role in the early postnatal period in thermoregulation has long been recognized (6,7). Several independent studies indicate that BAT persists into older childhood and adult life and remains physiologically relevant, as evidenced by its positive association with resting energy expenditure (8), skeletal muscle volume (9), and glucose regulation (10) as well as its negative association with body mass index (BMI) (8,11,12), total body fat (8,11), and visceral fat (11,13), thereby supporting a protective role of BAT against obesity.

Very little is known about the potential protective effects of BAT characteristics in early life on obesity/adiposity in subsequent periods of life, in part likely due to the lack of non-invasive, validated methods to assess BAT mass and BAT activity in newborns and infants. We recently reported on a non-invasive method to segment and quantify BAT composition in infants using magnetic resonance imaging (MRI) (14). In contrast to the unilocular adipocyte composition of WAT, BAT has multilocular adipocytes and is mitochondria- and capillary-dense. Therefore, the ratio of water to fat is greater in BAT compared with WAT, making it ideally suited for chemical shift imaging. Fat protons resonate at a frequency of 3.5 ppm higher than water; therefore, BAT can be differentiated from WAT spectroscopically (15). Chemical shift imaging takes advantage of the frequency difference, or chemical shift, by observing the contributions of differing

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phase on the overall signal contribution (16,17). This method has now been validated in rodents (18) and through post-mortem histological verification of BAT deposits in a 3-month-old infant (19). Fat signal fraction (FF, the ratio of fat-based signal to the sum of combined water- and fat-based signal) mapping has more recently been used to characterize the depletion of fat stores in BAT depots of hypothermic newborns (20) and to demonstrate BAT composition differences between obese and normal-weight children (21,22). To our knowledge, normative values of FF in the first year of life have been limited to our previously mentioned work (14) and one cross-sectional report of 12 infants (1–171-days old) (21).

Thus, the goal of the current study was to characterize BAT at birth in a population of healthy human newborns, and to examine the association between newborn BAT characteristics and body composition over the first 6 months of life (as measured using Dual X-ray absorptiometry (DXA)). Numerous studies provide evidence that child size and growth velocity particularly during the early period of infancy (first months of postnatal life) are among the strongest predictors of childhood obesity. Increased size or rapid weight or fat gain during this early postnatal growth phase is associated with increased risk for childhood (and adult) obesity (23–26) as well as with other related outcomes including metabolic risk (27), hypertension, and asthma in later life (28,29).

METHODS

Participants

Study participants comprised a cohort of children followed up prospectively from intrauterine life and birth through infancy at the University of California, Irvine, Development, Health and Disease Research Program in Orange, CA. Pregnant mothers were recruited between 2011 and 2015 in early gestation from obstetric care provider clinics. Exclusion criteria for pregnant mothers were multiple pregnancies, uterine or cervical abnormalities, or conditions associated with dysregulated neuroendocrine and immune function such as endocrine, hepatic, or renal disorders or corticosteroid medication use. Exclusion criteria for children (newborns) were preterm delivery at <34 weeks' gestation, perinatal complications associated with neurological consequences (e.g., hypoxia), and congenital, genetic, or neurological disorders (e.g., fetal alcohol syndrome, Down's syndrome, or other aneuploidies, such as fragile X syndrome). All pregnant mothers who met the inclusion/exclusion criteria at the study clinics were approached consecutively. The final sample for the current analyses consisted of 35 infants. In all, 57% ($N=20$) of the children were girls. The characteristics of the study population are presented in **Table 1**. All babies included in this study were born to mothers with uncomplicated pregnancies (no major medical conditions) and were healthy at the time of birth. A total of $N=3$ infants were born between weeks 34 and 37 (late preterm), and $N=4$ infants were small-for-gestational age (SGA, birth weight <the 10th percentile for gestational age, $N=1$ overlap between late preterm and SGA). All the study procedures were approved by the UC Irvine Institutional Review Board, and all mothers provided a written informed consent.

MRI to Assess BAT Characteristics

MRI was performed on a Siemens 3T Tim Trio system (VB17 software) using a 12-channel head coil and neck coils. Scans were conducted using a previously validated chemical-shift three-dimensional gradient echo Dixon method (Repetition Time = 7.47 ms, TE1/TE2 = 2.45/3.675 ms, NA = 1, Bandwidth/pixel = 977 Hz, Flip Angle = 10, matrix = 512 × 320 × 160, 0.97 × 0.97 × 1 mm, scan time = 3 min 2 s) (14). Regions of interest were defined as the combination of supraclavicular and axillary deposits and segmented using a semi-automatic procedure as previously described in detail (**Figure 1**) (14). Seed points for active contour segmentation were manually placed in deposits in supraclavicular and axillary regions. Seed bubbles of 3 mm were used to roughly cover these areas while avoiding any subcutaneous WAT partial volume regions. Supraclavicular and axillary ROIs were limited to four seed points per side to ensure consistent definition. The active contour evolution was iterated until the contours were visually covered by label, between 40 and 50 iterations. The supraclavicular/axillary region was chosen as it is a well-documented site for BAT, and the union of supraclavicular and axillary deposits has been shown to be the most repeatable region of BAT measurement in human neonates (14). The FF was averaged across all voxels within the individualized bilateral masks, resulting in a single reported measure for each individual. Higher fat fraction values are believed to reflect a fattier composition (less BAT-like) and have been associated with the obese state in children (21,22). Furthermore, cooling–reheating protocols have demonstrated decreases in BAT FF as a result of lipid consumption during cold exposure (30).

Table 1. Maternal and infant characteristics

Maternal characteristics	
Pre-pregnancy BMI (mean ± SD)	28.05 ± 7.20
Gestational weight gain (kg, mean ± SD)	13.42 ± 7.69
Infant characteristics	
Sex (females)	57%
Gestational age at birth (weeks, mean ± SD)	38.98 ± 1.44
Birth weight (g, mean ± SD)	3,274.49 ± 561.07
Feeding status (exclusively breastfed until 6 months age)	33%
Race/ethnicity	
Hispanic White	40%
Hispanic other race	34%
Non-Hispanic White	14%
Non-Hispanic other race	12%

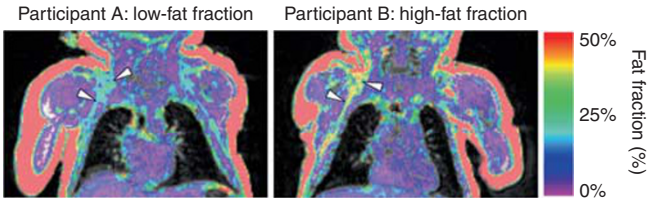

Figure 1. Example BAT fat fraction images. Example of participants with relatively low (left) and high fat fraction (right) are shown. The fat fraction (ratio of fat signal to the sum of fat and water) image is displayed on top of an anatomical image (sum of fat and water). Top and bottom white arrows indicate supraclavicular and axillary fat depots, respectively. BAT, brown adipose tissue.

Infants were, on average, about 1-month old at the time of the MRI scan (26 ± 13 mean (± SD) days). Age at the time of MRI scan and gestational age at birth were not associated with the mean BAT FF.

Dual-Energy X-Ray Absorptiometry to Assess Body Composition

A whole-body DXA scan was obtained using a Hologic Discovery Scanner (A, QDR 4500 series, Hologic, Bedford, MA) in a pediatric scan mode. Calibration using Hologic's anthropomorphic Spine QC Phantom was performed before each scan. During the scan, infants lay supine while sleeping, wearing only a disposable diaper and swaddled in a light cotton blanket. If the baby moved during the scan, a single repeat was performed once the baby had been pacified. At the time of the newborn DXA assessment, children were, on average, 25.7 days old (mean (±11.6 (SD) days). The second DXA assessment was conducted, on average, at 6 months of life (6.3 ± 0.46 mean (± SD) months). As older age at the DXA scan of the newborn but not at the DXA scan of the 6-month-old infant was positively associated with total percent body fat (%BF), we used an age-adjusted newborn measure of %BF in the analyses. Adiposity gain was defined as the difference between the age-adjusted newborn %BF and %BF at 6 months of life.

Infant Feeding

The infant feeding method (breast- or formula-feeding) was assessed by maternal interviews at the newborn's and 6-month-old's DXA assessment. All babies were exclusively breastfed at the time of the newborn DXA assessment. To control for infant-feeding status over the 6-month postnatal period, a variable was computed indexing whether or not the mother continuously breastfed the child until 6 months of life.

Maternal Anthropometrics, Birth Outcomes, and Sociodemographic Characteristics

Maternal sociodemographic characteristics (age, education, income, parity, and race/ethnicity) were obtained by a standardized structured interview at the first pregnancy visit. Race/ethnicity was determined by self-report using the Office of Management and Budget 1997 Revisions to the Standards for the Classification of Federal Data on Race and Ethnicity (Revision of Statistical Policy Directive No. 15, Race and Ethnic Standards for Federal Statistics and Administrative Reporting). Maternal pre-pregnancy BMI (weight in kg/height in m^2) was computed based on pre-pregnancy weight abstracted from the medical record and maternal height measured at the research laboratory during the first pregnancy visit. Maternal weight at delivery was abstracted from the medical record. Total gestational weight gain was calculated by subtracting the pre-pregnancy weight from weight at delivery.

Birth outcomes, including gestational age at birth and newborn's birth weight, were abstracted from the medical record.

Statistical Analyses

The distributions of continuous variables included in the analyses were tested for normality (Kolmogorov–Smirnov test). All continuous variables were normally distributed ($P > 0.200$ for null hypothesis). Pearson product–moment correlations were used to test bivariate associations between the mean BAT FF and other variables (maternal pre-pregnancy BMI, weight gain during pregnancy, gestational age at birth, birth weight adjusted for length of gestation, age at scan, and infant sex). Differences in BAT FF concentrations between different racial/ethnic groups were tested using a univarite ANOVA. Multiple linear regression was used to quantify the association between BAT FF and change in %BF gain, with and without adjustment for the effects of gestational weight and pre-pregnancy BMI, infant sex, infant-feeding status, and SGA status because these factors have been shown to be associated with gain in infant adiposity in previous studies.

Diagnostics were performed to assess the validity of standard linear regression assumptions. No extreme departures from general assumptions were observed, and no observations were removed from the analysis. All statistical analyses were performed using SPSS v21 (IBM Corp., Version 21.0. Armonk, NY, USA), and the statistical significance level was set at $\alpha = 0.05$.

RESULTS

The mean BAT FF in neonates was 29.4 ±4.06% (SD), and ranged from 22.9 to 36.4%, consistent with previous reports of neonatal supraclavicular BAT FF (14,21). The mean %BF at birth and at 6 months of age was 13.8 ± 4.7 (range: 2.2–27) and 32.6 ± 9.0 (range: 16.8–48.3), respectively. The average change in %BF from 0 to 6 months of age was 18.8 ± 8.5 (range: 5.6–37.6).

There was no significant association between BAT FF and newborn %BF ((unstandardized) β (95% confidence interval (CI)) = −0.180 (−0.519 to 0.285), $r = 0.154$, $P = 0.295$). There was a significant association between newborn BAT FF and change in %BF from 0 to 6 months of age. In unadjusted analyses, a lower BAT FF (more "brown fat-like" composition) was associated with a smaller change in %BF from 0 to 6 months (β (95% CI) = 0.893 (0.236–1.550), $r = 0.428$, $P = 0.009$, **Figure 2**), and lower %BF at 6 months of age (β (95% CI) = 0.797 (0.048–1.503), $r = 0.348$, $P = 0.037$). These effects persisted after adjusting for maternal pre-pregnancy BMI, maternal gestational weight gain, infant sex, and SGA and infant-feeding status (β (95% CI) = 0.951 (0.293–1.610), (partial) $r = 0.492$, $P = 0.006$) for adjusted effect of BAT FF on change in %BF from 0 to 6 months, and β (95% CI) = 0.974 (0.302–1.646; partial) $r = 0.489$, $P = 0.006$ for adjusted effect of BAT FF on %BF at 6 months). Specifically, in the adjusted model, a one SD unit decrease in newborn BAT FF was associated with an ~20% reduction of the average increase in %BF gain from 0 to 6 months of age. Statistical coefficients for

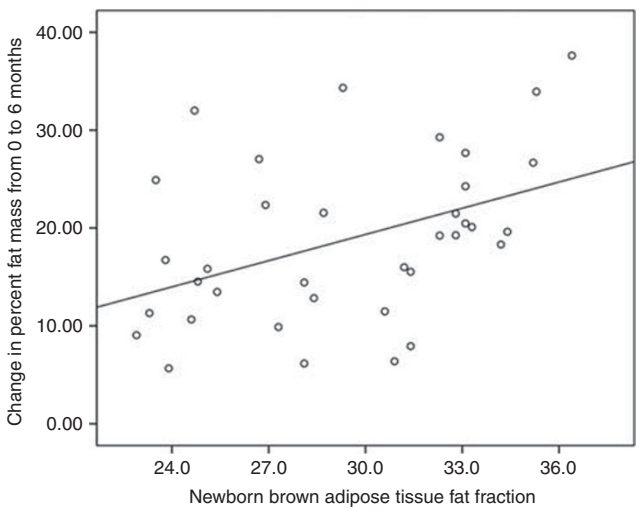

Figure 2. Newborn BAT FF is prospectively associated with 0–6-month adiposity gain. Newborn supraclavicular brown adipose fat fraction (measured with magnetic resonance imaging) and change in percent body fat (measured by dual-energy X-ray absorptiometry) from 0 to 6 months of age. Higher fat fraction is indicative of a fattier (less BAT-like) composition. BAT, brown adipose tissue.

Table 2. Statistical coefficients of the different models for the effect of BAT FF on infant body composition

	β (95% CI)		
	%BF newborn age	%BF at 6 months age	change in %BF from 0 to 6 months of age
BAT FF (unadjusted)	−0.180 (−0.519 to 0.285) $P=0.295$	0.893 (0.236 to 1.550) $P=0.009$	0.797 (0.048 to 1.503) $P=0.037$
BAT FF (adjusted)[a]	0.023 (−0.367 to 0.413) $P=0.905$	0.974 (0.302 to 1.646) $P=0.006$	0.951 (0.293 to 1.610) $P=0.006$

%BF, percent body fat; BAT FF, brown adipose tissue fat fraction; CI, confidence interval.
[a]Adjusted for maternal pre-pregnancy BMI, maternal gestational weight gain, infant sex, small for gestational age, and infant-feeding status.

the unadjusted and adjusted models are summarized in Table 2.

The mean BAT FF was not significantly associated with birth weight, birth weight percentile, or weight at 6 month (all r values < -0.132, P values > 0.444).

DISCUSSION

The current study represents, to the best of our knowledge, the first report in humans linking higher brown fat-like composition of newborn supraclavicular fat depot (a primary location of brown fat) with a smaller increase in infant total body fat from birth till 6 months of age (a key indicator of increased childhood and adult obesity risk (23–26)). This effect persisted after adjusting for other potential determinants of newborn and infant %BF and change in %BF. The magnitude of the effect translates to an ~20% reduction of the average increase in %BF gain from 0 to 6 months of age per SD decrease in newborn BAT FF. We suggest that the magnitude of this effect is substantial, particularly for a single factor, considering that in a recent publication (31) a combined set of several factors including race, gestational weight gain, pre-pregnancy BMI, feeding patterns, gestational age at birth, and sex accounted for 19% in the variance of adiposity (% body fat) at birth.

Lower BAT FF values are believed to reflect a more BAT-like composition of fat depots and have been associated with lower obesity risk in children (21,22). The effect observed in the current study may therefore be mediated by the capacity of the more brown-like fat composition to facilitate energy expenditure via lipid metabolism and thermogenesis pathways during the first month of life, thereby reducing white fat deposition from 0 to 6 months of age.

In the current study BAT FF was not associated with newborn %BF. This may be due to the relatively short duration of *ex utero* thermal exposure at the time of scan (average 26 days after birth) or the relatively limited interindividual variability in newborn fat stores. Whereas BAT and WAT deposition occurs *in utero*, non-shivering thermogenesis (that is necessary for stimulating BAT) does not begin until the neonate is born and exposed to the relatively cold *ex utero* environment. Therefore, the effective exposure time to *ex utero* conditions, and its consequences on BAT lipid content, are minimal in the newborn period.

The limitations of this study include the use of a dual-echo acquisition rather than a multiecho acquisition and the lack of a measure for BAT activity. This acquisition method lacks the multiple echo points needed for full characterization of the complex lipid profile. In theory, this limits the measurement by having an imperfect water–fat separation within the BAT depots. However, the utility of the dual-echo approach has been demonstrated in previous *in vivo* human BAT MRI (14,32,33), and it has been shown that the use of a dual-echo, vs. a multiecho, acquisition primarily adds a uniform bias relative to MR spectroscopic measurement of hepatic fat fraction (34). Finally, it should be noted that because of the spatial resolution limits of MRI and the interspersed distribution of brown fat cells found in humans, all of the depots measured in this work may contain a partial volume average of brown/beige and white fat cells.

The issue of the physiological relevance of BAT FF within these depots warrants further study. First, while the supraclavicular region has demonstrated functional plasticity through positive UCP1 expression in both BAT-active and -inactive adults (35), our current method is unable to determine whether the neonatal supraclavicular depot exhibits the same physiological properties. Prior evidence suggests a distinct second type of human BAT found in the interscapular region of newborn humans (32). Second, we note that this is a measure of BAT composition and not activity. The FF can then be thought of as either reflective of BAT capacity for future energy expenditure (lower FF is due to greater mitochondrial density) or suggestive of past lipid metabolism (lower FF is due to lipid stores having been utilized) (30). Certainly, these two physiological properties are not uncoupled, and future work is needed to gain a better understanding of the physiological underpinnings of BAT FF. Future studies also are warranted that incorporate measures of BAT characteristics at 6 months of age, as well as concurrent measures of energy expenditure and metabolic function, and also perform longitudinal follow-up to quantify changes in BAT characteristics from birth to infancy, childhood, and beyond, along with the concurrent characterization of other infant and child phenotypes of interest in healthy as well as clinical (e.g., SGA) populations.

Our findings may provide the basis for important clinical applications. BAT may provide a pharmacological target in the context of the growing problem of obesity (8,11,12,36,37). Recent studies suggest that brown-in-white or beige tissue can be induced from WAT through stimulation (38,39). Thus, potentially altering (optimizing) the initial amount of BAT or BRITE tissue in newborns, and its subsequent rate of attrition during infancy and childhood may serve as a primary

prevention strategy against the development of obesity and metabolic dysfunction.

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