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Changes in Brown Adipose Tissue in Boys and Girls during Childhood and Puberty

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Abstract

Objective—To characterize the changes in brown adipose tissue (BAT) during puberty in boys and girls.

Study design—We examined the prevalence and the volume of BAT at different stages of sexual development in pediatric patients who underwent positron emission tomography/computer tomography (PET/CT) studies.

Results—Of the 73 patients, 43 (59%) had BAT depicted on PET/CT. Visualized BAT was significantly less prevalent in PET/CT studies of pre-pubertal (Tanner stage 1) children than pubertal (Tanner stages 2-5) subjects (15% vs. 75%). Values for the volume of BAT also increased during puberty, but the magnitude of the increase was substantially greater during the final two stages of puberty (Tanner stage 4 or 5) than in earlier stages of sexual development (Tanner stages 1, 2, and 3) (Boys: 499±246 vs. 50±36, $p < 0.0001$, Girls: 286±139 vs. 36±29, $p = 0.024$). Changes in BAT volume were also significantly greater in boys than in girls ($p = 0.004$) and were closely related to muscle volume (r 's = 0.52, 0.64 and both p 's < 0.01, for boys and girls, respectively).

Conclusion—The depiction and the volume of brown fat increase during puberty. Metabolic and hormonal events related to the achievement of sexual maturity are likely responsible for the rapid increase in brown fat that occurs during puberty.

Keywords

Brown adipose tissue; puberty; muscle; PET/CT

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The adipose organ is a complex endocrine system, composed of white and brown adipose tissue (BAT). White adipose tissue serves as the primary site of energy storage, storing triglycerides within individual adipocytes, and BAT stores little fat, burning it instead to produce heat and regulate body temperature (1-4). In comparison with white fat, which has been extensively studied in recent years, relatively little progress has been made in our understanding of brown fat. The lack of reliable methods to quantify BAT in humans has greatly limited our understanding of the physiologic role of this tissue.

Based on anatomical studies, BAT was known to be present in all neonates but thought to be lost after infancy (3). However, significant amounts of BAT have recently been noticed in a fraction of patients undergoing positron emission tomography/computed tomography (PET/CT) examinations (1, 5). To date, clinical studies have been mostly confined to the use of fluoro-deoxyglucose (FDG) that is taken up by metabolically active BAT (6). The depiction of BAT by PET has been reported to be dependent on a multitude of physiologic and technical factors including age, sex, body composition, FDG dose, acquisition parameters, and season and temperature during examinations (1, 2, 7-11). Moreover, PET scans underestimate the amount of BAT because they only reflect metabolically active tissue (12-14). Recently, it has been shown that cytological differences between brown and white adipocytes translate into differences in radiographic attenuation and that BAT is characterized by significantly higher CT Hounsfield Units (HU) than white fat (15). Differences in HUs and FDG uptake between these two adipose tissues allows for measurement of BAT using both the CT and PET components of PET/CT scans.

We have previously shown that pediatric patients with visualized BAT on PET/CT examinations had significantly greater muscle volume than patients with no identifiable BAT (16). This clinical observation is consistent with data from cell cultures indicating that brown adipocytes and myocytes may derive from a common lineage in the paraxial mesoderm (17, 18) and that muscle and some brown fat cells express myogenic factors, such as Myf5 (19). Further support for a link between brown fat and skeletal muscle comes from knowledge that these tissues share many features such as an abundance of mitochondria, energy expenditure via oxidative phosphorylation, and sympathetically mediated adaptive thermogenesis (20, 21).

Regardless of sex, skeletal musculature increases substantially during puberty. Gains in musculature associated with sexual development closely equal the growth of all other organs, systems and tissues combined (22). To test the hypothesis that measures of BAT, like those of muscle, increase during puberty, we examined the changes in BAT at various stages of sexual development in 73 pediatric patients undergoing follow-up PET/CT examinations and found to have no evidence of disease.

METHODS

The study subjects were patients seen regularly by the division of Hematology and Oncology at Children's Hospital Los Angeles. This study was compliant with the Health Insurance Portability and Accountability Act and the investigational protocol was approved by the Institutional Review Board for clinical investigations at this facility; informed consent was waived because all imaging was performed for clinical purposes. The study subjects comprise 38 males and 35 females, ages 4 to 19.9 years old who had been treated previously for pediatric malignancy but were disease free at the time of examination. Of the 73 patients, 57 had lymphoma (42 Hodgkin's, 6 B-cell, 5 Burkitt's, 2 anaplastic large cell, 1 lymphoblastic lymphoma, 1 lymphoma), 4 had neuroblastoma, 3 had acute lymphoblastic leukemia, 2 had cancer ruled out and 7 had one of the following: Castleman Syndrome, Ewing's sarcoma, medullablastoma, melanoma, rhabdomyosarcoma, post-transplant

lymphoproliferative disorder, and thyroid cancer. Although many study subjects (46 out of 73) have been the basis of previous investigations (15, 16), for the purpose of this study, only the last follow-up examination of patients free of disease with normal PET/CT studies were analyzed. Age, height, and weight measures were obtained at the time of each PET/CT examination. Body mass index (BMI) was calculated as weight in kilograms divided by the square of the height in meters, and BMI % was calculated via the Centers for Disease Control and Prevention's calculator (<http://apps.nccd.cdc.gov/dnpabmi/Calculator.aspx>).

PET/CT scans were performed on a Gemini system (Philips Healthcare, GXL Release 3.3, Cleveland, Ohio) in patients after 12 hours fasting. Patients were injected with fluoro-deoxyglucose between 2.4 and 13.6 mCuries, depending on body weight (0.14 mCi/kg) (23). All studies were performed after intravenous and oral contrast (meglumine diatrizoate, Gastrografin, Bristol-Myers Squibb, New York, New York) enhancement. No muscle relaxants or additional agents were administered, and all patients were indoors in room temperature (22°C) for at least two hours before examination. Total acquisition time for each study was 1 hour. The axial in-plane spatial resolutions for PET and CT slices were 4 and 1.17 mm, respectively, and the slice thicknesses were 4 and 5 mm, respectively.

Testicular volume determinations were obtained using CT measures of the length, width, and height of the gonad and the formula for an ellipsoid. Emphasis was placed on using the larger of the testes. For the purpose of this study values for testicular volume were used to determine the Tanner stage of sexual development (24); Tanner 2 $\geq 4\text{cm}^3$, Tanner 3 $\geq 9\text{cm}^3$, Tanner 4 $\geq 13\text{cm}^3$, Tanner 5 $\geq 20\text{cm}^3$. The CVs for repeated measurements of testicular volume using CT was calculated to be 4.3%. The three dimensional images of the whole-body CT study were used by a pediatric endocrinologist to assess the degree of breast development to determine the Tanner stage in girls. For the purpose of this study, Tanner 2 and 3 were defined by the presence of a small and large breast bud, respectively; Tanner 4 was defined by the additional projection of the areola and papilla to form a secondary mound above the level of the breast, and a mature breast with projection of papilla only represented Tanner 5. Although determinations of the Tanner stage did not include breast palpation, available data indicate that the use of pictures allows for accurate assessment of Tanner stage, even when the assessment is done by adolescent girls themselves (25-29).

All PET/CT examinations were reviewed independently by two radiologists to determine the presence or absence of metabolically active BAT. A patient was considered to have BAT when both radiologists diagnosed its presence. Studies with discrepant assessments were re-evaluated by both radiologists together to arrive at a consensus. The radiologists also assured that the underlying CT Hounsfield units (HU) were negative and indicative of fat tissue density and that the ROIs were exclusive of muscles and other tissue boundaries. The distributions of HUs from the CT and PET standardized uptake values (SUV) within these BAT-visualized areas were then measured and tabulated to calculate the volume of BAT (cm^3) from the first cervical vertebrae to the pubic bones. Even though HU values for brown fat are significantly higher than those of white fat and uptakes of these two adipose tissues do not overlap at levels greater than 1.5 (15), we used thresholds of one SD above the mean HU and an SUV greater than 1.5 to calculate the volume of BAT.

Muscle and fat tissue volumes were measured semi-quantitatively on the basis of CT Hounsfield units (HU) using an offline computer workstation running SliceOmatic image segmentation software (Tomovision, Inc., Quebec, Canada). In brief, the volume of abdominal musculature (rectus muscles, oblique muscles, lumbar quadrate muscles, psoas muscles, and erector muscles of the spine) was determined by measuring all voxels with positive HU values (excluding bone, viscera, vessels and bowel) in a 2.5 cm section at the level of the umbilicus. At the same locations and from the same CT images, measurements

of subcutaneous abdominal fat (SAF) and intra-abdominal fat (IAF) were obtained by measuring all voxels with negative HU values (excluding air in bowel). For the purposes of this study, SAF was defined as the volume in cm³ of adipose tissue located between the skin and the rectus muscles, the external oblique muscles, lumbar quadratus muscles, and the erector muscles of the spine, and IAF was defined as the intra-abdominal adipose tissue surrounded by the rectus muscles, the oblique muscles, the lumbar quadratus muscle, the psoas muscles, and the vertebral body at the same site. The CVs for CT measures of trunk musculature, SAF and IAF have been reported to be between 1.5% to 3.5% (30).

STATISTICAL ANALYSIS

Statistical analysis was carried out with Statview software (version 5.0.1; SAS Institute, Cary, North Carolina) by using t test for unpaired samples and simple, multiple, and logistic linear regression analyses. In most models, the volume or presence of BAT was used as the outcome variable, and anthropometric measures, season (defined as winter versus other seasons), treatment with corticosteroids, and Tanner stage were used as possible independent variables. To exclude the possibility of multicollinearity on the multiple regression models, postestimation procedures were used to calculate a condition number for the regression models and comparing the condition number with the suggested cutoff value of 15 (31). The goodness of fit for the regression models was evaluated with the post-estimation procedures of STATA (StataCorp, College Station, Texas). All models presented passed the following goodness of fit criteria: residuals appeared random and no strong influence or leverage points were present, on the basis of both a graphical and distribution evaluation. All values are expressed as means plus or minus standard deviation (SD).

RESULTS

Of the 73 patients, 43 (20 girls, 23 boys) had visible BAT. Although BAT-visualized cases were observed in all months except May and June, there were more occurrences during November to January than the remaining months; 22 of 27 vs. 21 of 46; $p = 0.003$. There were no significant sex differences in the prevalence of PET/CT studies depicting BAT; 20 of 35 (57%) girls vs. 23 of 38 (60%) boys, $p = 0.769$. Both males and females with visualized BAT tended to be older, more sexually developed, taller, and more muscular than those without visualized BAT. In males, values for weight also differed between patients with and without BAT. In contrast, there were no differences in the BMI percentiles or measures of subcutaneous and visceral adiposity (Table I).

Figure 1 shows the proportions of studies depicting BAT according to the stage of sexual development. BAT was significantly less prevalent in pre-pubertal (Tanner stage 1) girls and boys than during adolescence (Tanners 2-5). Multiple logistic regression analysis also confirmed the independent positive effects of the degree of sexual development on the presence or absence of BAT, even after adjusting for sex, BMI %, treatment, and season (Table II). This was true whether all Tanner stages were included in the model independently or whether they were divided into pre-pubertal and pubertal.

Regardless of sex, volumes of BAT increase with age and the level of sexual development (Figure 2). Increases in BAT volumes were, however, substantially greater during the final two stages of puberty. Whereas volumes of BAT did not significantly differ among Tanner stages 1, 2, and 3, values were substantially greater during Tanner stage 4 and 5 in both males and females (Figure 2, B). However, the volume of BAT was significantly greater in males than females during the last stages of puberty ($p=0.004$). Multiple regression analysis confirmed the independent positive effect of pubertal stage and sex on BAT volume even after adjusting for BMI%, treatment, and season (Table II). This was true whether all Tanner

stages were included in the model independently or whether they were divided into early puberty (Tanner stages 1-3) and late puberty (Tanner stages 4-5).

As expected, muscle volumes were highly correlated with Tanner stage ($r=0.86$ and $r=0.81$ for males and females respectively; both $p<0.0001$). The volume of muscle, like that of BAT, also preferentially increased in the late stages of puberty. There were significant relations between BAT and abdominal musculature (Figure 3; available at www.jpeds.com). This was true whether the volume of BAT ($r = 0.52$ and $r = 0.64$, for males and females; both p 's <0.01) or the presence of BAT ($r = 0.56$ and $r = 0.48$, for males and females; both p 's <0.01) was used in the analysis.

DISCUSSION

Our results are in agreement with studies showing a higher prevalence of BAT depiction in pediatric PET/CT examinations (23, 32, 33) when compared with that of adult patients (1). They also support the finding by Gelfand et al that the incidence of brown fat uptake in adolescence and young adults is greater than in patients younger than 10 years (23). Consistent with previous studies indicating that accumulation of BAT is related to environmental temperature we found that, even in warmer climates, the presence of BAT is more common in studies during the winter months (11). Interestingly, although season (temperature) predicted the depiction of BAT, it did not influence the volume of BAT, a finding that supports the notion that BAT is present, but dormant, in most humans. Indeed, BAT activity is observed in most subjects during cold exposure but not under thermoneutral conditions (33-36).

Even though several studies in adult patients have found BAT to be more prevalent in women (1, 7-11), we found that values for BAT volume were greater in boys than girls. However, recent evidence suggests that the higher prevalence and greater volume of BAT in females when compared with males is only present in middle aged and elderly subjects (8). The factors related to the pubertal increases and sexual dimorphism in the amount of BAT have not been explained. Changes in BAT during sexual development were, however, closely related to gains in muscle volume in both boys and girls. The maximal volume of BAT, like that of muscle, occurs relatively late and follows chronologically the maximal growth in height (22). This observation further supports the notion of a strong connection between brown adipocytes and myocytes (17, 18, 20, 21). Thus, regardless of the mechanism(s) involved in BAT accumulation during sexual development, both brown fat and muscle are predicted by pubertal stage and sex. Numerous metabolic and hormonal changes occur during puberty, including increases in the production of growth hormone/ growth factors, gonadotropins, and sex steroid hormones. Variations in one or more of these important modifiers known to influence muscle development could also account for the increases and sex dimorphism in brown fat during adolescence. Indeed, recent data suggest that sex hormones have a marked effect on BAT activity; receptor expression differs in cell-cultured brown adipocytes of male and female rodents with higher numbers of all receptor types in male BAT (37).

This study has notable, but unavoidable limitations. It is based on a retrospective, cross-sectional analysis of follow-up PET/CT examinations of children treated for malignancy. Due to its retrospective nature, we could not control for all potential differences in exposure to temperature such as differences in clothing between pre-pubertal and adolescent boys and girls. Unfortunately, no technique is currently available for safe prospective examinations of BAT in healthy pediatric populations. To date most children with cancer can, however, be expected to have survival rates greater than 85% (38) and by selecting disease free patients, the bias associated with not recruiting healthy subjects is somewhat minimized. Another

major limitation is that most subjects were treated with high doses of glucocorticoids, known to promote central adiposity and cause muscular atrophy (39). Although we found no significant differences in the measures of subcutaneous or visceral adiposity between patients with and without functioning BAT, examining the relation between the amount of BAT and other adipose tissue following treatment with corticosteroids would be prone to error. However, finding an association between BAT and muscle in patients successfully treated for pediatric lymphoma underscores the strength of the link between these two tissues.

In humans, the greatest gains in skeletal muscle occur during the fetal stage, infancy and puberty (22). Concurrently, all fetus and newborns have BAT (1), and as the results of the current imaging study strongly indicate, large amounts of brown fat are also present during adolescence. Although the reasons for the pubertal increase in BAT are unknown, careful metabolic and endocrinologic evaluations of normal adolescents may facilitate the identification of the factors responsible not only for the rapid increase in brown fat that occurs during puberty but also for sex differences in BAT. The recent development of non-invasive magnetic resonance imaging techniques to characterize BAT could greatly aid to our understanding of the contributions of this important tissue in regulating human physiology (40).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Bar graphs showing the percentage of pre-pubertal (Tanner 1) and pubertal (Tanner 2-5) male and female subjects depicting BAT. There is a statistical significant difference in the percentage of subjects depicting BAT between pre-pubertal (0%) and pubertal (67%) females (* $P=0.005$) and between pre-pubertal (20%) and pubertal (87%) males (** $P<0.0001$)

Figure 2.

A, Relations between the volume of BAT and age in 43 male and female subjects with visualized BAT. The linear coefficients were $r=0.77$ and 0.72 for males and females, respectively; both P 's <0.001 . **B,** Relations between the volume of BAT and Tanner stage in 43 male and female subjects with visualized BAT. The linear coefficients were $r=0.70$ and 0.54 for males and females, respectively; both P 's ≤ 0.01

Figure 3.

Relations between the volume of BAT and the volume of trunk muscle in 43 male and female subjects with visualized BAT. The linear coefficients were $r=0.52$ and 0.64 for males and females, respectively; both P 's < 0.01 .

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Table 2

Multiple Logistic and Linear Regression Models for the Prediction of BAT

<i>BAT</i> +/-*	β	Std. Error	P-value	R ²
Tanner stage	0.920	0.222	<0.0001	
Sex	1.268	0.727	0.081	
BMI%	-0.003	0.011	0.803	0.352
Season	1.497	0.716	0.037	
Treatment	-0.362	0.703	0.607	

<i>BAT</i> volume**	β	Std. Error	P-value	R ²
Tanner stage	0.647	23.55	<0.0001	
Sex	0.342	59.50	0.010	
BMI %	0.182	0.968	0.131	0.509
Season	0.113	55.95	0.342	
Treatment	0.057	65.92	0.641	

* Analysis obtained using 73 subjects

** Analysis obtained using 43 subjects with visualized BAT