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

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

Study design We examined the prevalence and the volume of BAT at different stages of sexual development in 73 pediatric patients who underwent positron emission tomography (PET)/computed tomography (CT) studies.

Results Of the 73 patients studied, 43 (59%) had BAT depicted on PET/CT. The presence of BAT was detected significantly less frequently on PET/CT in prepubertal subjects (Tanner stage 1) than in pubertal subjects (Tanner stages 2-5) (15% vs 75%). BAT volume also increased during puberty, with a significantly greater magnitude of the increase in the final 2 stages of puberty (Tanner stages 4 and 5) than in earlier stages (Tanner stages 1-3) (boys: 499 ± 246 vs 50 ± 36, P < .0001; girls: 286 ± 139 vs 36 ± 29, P = .024). Changes in BAT volume were also significantly greater in boys than in girls (P = .004) and were closely related to muscle volume (r = 0.52, P < .01 for boys; r = 0.64, P < .01 for girls).

Conclusion The presence and volume of BAT increase rapidly during puberty. Metabolic and hormonal events related to the achievement of sexual maturity are likely responsible for this increase. (J Pediatr 2012;160:604-9).

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

Based on anatomic studies, BAT was known to be present in all neonates but thought to be lost after infancy.3 However, significant amounts of BAT were recently reported in a fraction of patients undergoing positron emission tomography (PET)/computed tomography (CT) examination.1,5 To date, clinical studies have been confined mostly to the use of fluorodeoxyglucose (FDG), which is taken up by metabolically active BAT.6 The depiction of BAT by PET reportedly depends on numerous physiological and technical factors, including age, sex, body composition, FDG dose, acquisition parameters, and season and temperature during the examination.1,2,7-11 Moreover, PET scans underestimate the amount of BAT because they reflect only metabolically active tissue.12-14 Recently, it has been shown that cytological differences between brown and white adipocytes translate into differences in radiographic attenuation, with BAT characterized by significantly higher numbers of CT Hounsfield units (HUs) than WAT.15 The differences in HU values and FDG uptake between WAT and BAT allow for measurement of BAT using both the PET and CT components of PET/CT scans.

We previously reported that pediatric patients with BAT visualized 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 mesoderm17,18 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 the fact that these tissues share many features, including 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 with 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 hospital’s Institutional Review Board for clinical investigations. The requirement for informed consent was waived because all imaging was performed for clinical purposes. The study cohort comprised 38 males and 35 females, aged 4-19.9 years, 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, 6 B-cell, 5 Burkitt, 2 anaplastic large cell, 1 lymphoblastic lymphoma, and 1 lymphoma), 4 had neuroblastoma, 3 had acute lymphoblastic leukemia, 2 had cancer ruled out, and 1 each had Castleman syndrome, Ewing sarcoma, medullablastoma, melanoma, rhabdomyosarcoma, posttransplantation lymphoproliferative disorder, and thyroid cancer. Although many of the study patients (46 of 73) have been subjects in previous investigations, in the present 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 percentile was calculated using 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 GXL PET/CT system (Philips Healthcare, Cleveland, Ohio) after a 12-hour fast. Patients were injected with 2.4-13.6 mCi of FDG, depending on body weight (0.14 mCi/kg). All studies were performed after i.v. 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 2 hours before the examination. The 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 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 this study, values for testicular volume were used to determine the Tanner stage of sexual development: 4 cm³, Tanner 2; 9 cm³, Tanner 3; 13 cm³, Tanner 4; 20 cm³, Tanner 5. The coefficient of variation for repeated measurements of testicular volume using CT was calculated as 4.3%. A pediatric endocrinologist used the 3-dimensional images of the whole-body CT study to assess the degree of breast development to determine the Tanner stage in girls. For this study, Tanner stages 2 and 3 were defined by the presence of small and large breast buds, respectively, Tanner stage 4 was defined by the additional projection of the areola and papilla to form a secondary mound above the level of the breast, and Tanner stage 5 was defined as a mature breast with projection of papilla only. Although the determination of Tanner stage did not include breast palpation, available data indicate that viewing pictures can provide an accurate assessment of Tanner stage, even when the assessment is done by adolescent girls themselves.

Two radiologists independently reviewed all PET/CT examinations 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 reevaluated by both radiologists together to arrive at a consensus. The radiologists also assured that the underlying CT HUs were negative and indicative of fat tissue density, and that the regions of interest were exclusive of muscles and other tissue boundaries. The distributions of HUs from the CT and PET standardized uptake values within these BAT-visualized areas were then measured and tabulated to calculate the volume of BAT (in cm³) from the first cervical vertebrae to the pubic bones. Even though HU values for BAT are significantly higher than those of WAT and uptakes of these 2 adipose tissues do not overlap at levels exceeding 1.5, we used thresholds of 1 SD above the mean HU and a standardized uptake value of >1.5 to calculate the volume of BAT.

Muscle and fat tissue volumes were measured semiquantitatively on the basis of CT HUs using an offline computer workstation running SliceOmatic image segmentation software (Tomovision, Quebec, Quebec, Canada). In brief, the volume of abdominal musculature (rectus muscles, oblique muscles, lumbar quadratus 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, external oblique muscles, lumbar quadratus muscles, and erector muscles of the spine, and IAF was defined as the intra-abdominal adipose tissue surrounded by the rectus muscles, oblique muscles, lumbar quadratus muscles, psoas muscles, and the vertebral body at the same site. Coefficients of variation of 1.5%-3.5% for CT measures of trunk musculature, SAF, and IAF have been reported.

Statistical analyses were performed with Statview version 5.0.1 (SAS Institute, Cary, North Carolina) using the Chi-square test, the 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...
Of the 73 patients, 43 (20 girls and 23 boys) had visible BAT. Although BAT-visualized cases were observed in all months except May and June, there were more occurrences between November and January than in the remaining months (22 of 27 vs. 21 of 46; \( P = .003 \)). There were no significant sex differences in the prevalence of PET/CT studies depicting BAT (20 of 35 girls [57\%] vs 23 of 38 boys [60\%]; \( P = .769 \)). Both the boys and girls with visualized BAT tended to be older, more sexually developed, taller, and more muscular than those without visualized BAT. In boys, weight also differed between patients with and without BAT, but BMI percentiles and measures of subcutaneous and visceral adiposity did not (Table I).

Figure 1 shows the proportions of studies depicting BAT according to stage of sexual development. BAT was significantly less prevalent in prepuberty (Tanner stage 1) than during adolescence (Tanner stages 2-5). Multiple logistic regression analysis also confirmed the independent positive effects of stage 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 were divided into prepubertal and pubertal categories.

Regardless of sex, BAT volume increased with age and stage of sexual development (Figure 2). Increases in BAT volumes were substantially greater during the final 2 stages of puberty, however. Whereas volumes of BAT did not differ significantly among Tanner stages 1, 2, and 3, values were substantially greater during Tanner stages 4 and 5 in both boys and girls (Figure 2, B). However, the volume of BAT was significantly greater in boys than in girls during the last stages of puberty (\( P = .004 \)). 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 were divided into early puberty (Tanner stages 1-3) and late puberty (Tanner stages 4 and 5).

As expected, muscle volume was highly correlated with Tanner stage (\( r = 0.86 \) for boys and \( r = 0.81 \) for girls; both \( P < .0001 \)). The volume of muscle, like that of BAT, increased preferentially in the late stages of puberty. There was a significant relationship between BAT and abdominal musculature (Figure 3; available at www.jpeds.com), regardless of whether the volume of BAT (\( r = 0.52 \) for boys and \( r = 0.64 \) for girls; both \( P < .01 \)) or the presence of BAT (\( r = 0.56 \) for boys and \( r = 0.48 \) for girls; both \( P < .01 \)) was used in the analysis.

### Discussion

Our results are in agreement with previous studies reporting a higher prevalence of BAT depiction in PET/CT examinations in children\(^{23,32,33}\) compared with adults.\(^1\) They also support the finding by Gelfand et al\(^{23}\) of a greater incidence of BAT uptake in adolescence and young adults than in children aged \( \leq 10 \) years. 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 conducted during the winter months.\(^{11}\) Interestingly, although season (ie, temperature) predicted the depiction of BAT, it did not influence the volume of BAT, supporting the idea 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 higher BAT volumes in boys than in girls. However, recent evidence suggests that the higher prevalence and greater volume of

| Table I. Age, anthropometric measures, and CT measures (mean ± SD) of muscle and fat in girls and boys who are BAT-positive and BAT-negative |
|-------------------------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Age, years                                      | 15.5 ± 3.0      | 10.6 ± 4.6      | .0005           | 15.1 ± 3.6      | 8.8 ± 3.7 | .0001 |
| Tanner stage                                    | 4.5 ± 0.8       | 2.6 ± 1.7       | .0001           | 3.8 ± 1.5       | 1.7 ± 1.4 | .0001 |
| Weight, kg                                      | 58.6 ± 21.4     | 45.0 ± 25.5     | .096            | 62.8 ± 22.2     | 35.9 ± 18.7 | .0004 |
| Height, cm                                      | 156.5 ± 11.5    | 136.8 ± 21.7    | .002            | 165.1 ± 19.6    | 127.6 ± 23.1 | .0001 |
| BMI\%                                           | 63.8 ± 25.5     | 72.5 ± 33.9     | .396            | 60.1 ± 34.7     | 69.3 ± 33.6 | .318 |
| Trunk muscle, cm\(^3\)                          | 259 ± 60        | 186 ± 81        | .004            | 302 ± 90        | 188 ± 75  | .025 |
| SAF, cm\(^2\)                                   | 604 ± 235       | 513 ± 403       | .492            | 482 ± 312       | 315 ± 334  | .128 |
| IAF, cm\(^2\)                                   | 85 ± 63         | 74 ± 46         | .590            | 91 ± 52         | 57 ± 63   | .078 |

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BAT in females is present only in middle-aged and elderly subjects. The factors related to the pubertal increases and sexual dimorphism in BAT volume have not yet been explained. Changes in BAT during sexual development were 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. This observation further supports the notion of a strong connection between brown adipocytes and myocytes. Thus, regardless of the mechanism(s) involved in BAT accumulation during sexual development, both BAT 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 sexual dimorphism in BAT 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.

This study has some notable, but unavoidable, limitations. It is based on a retrospective, cross-sectional analysis of follow-up PET/CT examinations of children treated for malignancy. Because of its retrospective nature, we could not control for all potential differences in exposure to temperature, such as differences in clothing, between prepubertal and adolescent boys and girls. Unfortunately, there is no available technique for safe prospective examination of BAT in healthy pediatric populations. Currently, however, children with most cancers can be expected to have a survival rate of >85%, and by selecting disease-free patients, the bias associated with not recruiting healthy subjects is minimized somewhat. Another major limitation is that most subjects were treated with high doses of glucocorticoids, which are known to promote central adiposity and cause muscular atrophy. Although we found no significant differences in the measures of subcutaneous or visceral adiposity between patients with and without functioning BAT, examining the relationship between the volume of BAT and the volume of other adipose tissue after corticosteroid treatment would be

### Table II. Multiple logistic and linear regression models for the prediction of BAT

<table>
<thead>
<tr>
<th>Model</th>
<th>( \beta )</th>
<th>SE</th>
<th>( P ) value</th>
<th>( R^2 )</th>
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</thead>
<tbody>
<tr>
<td>BAT-positive/-negative*</td>
<td>Tanner stage</td>
<td>0.920</td>
<td>0.222</td>
<td>&lt;.0001</td>
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<td></td>
<td>Sex</td>
<td>1.268</td>
<td>0.727</td>
<td>.081</td>
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<td></td>
<td>BMI%</td>
<td>-0.003</td>
<td>0.011</td>
<td>.803</td>
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<tr>
<td></td>
<td>Season</td>
<td>1.497</td>
<td>0.716</td>
<td>.037</td>
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<tr>
<td></td>
<td>Treatment</td>
<td>-0.362</td>
<td>0.703</td>
<td>.607</td>
</tr>
<tr>
<td>BAT volume†</td>
<td>Tanner stage</td>
<td>0.647</td>
<td>23.55</td>
<td>&lt;.0001</td>
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<tr>
<td></td>
<td>Sex</td>
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<td>.100</td>
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<tr>
<td></td>
<td>BMI%</td>
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<td>0.968</td>
<td>.131</td>
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<tr>
<td></td>
<td>Season</td>
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<td>55.95</td>
<td>.342</td>
</tr>
<tr>
<td></td>
<td>Treatment</td>
<td>0.057</td>
<td>65.92</td>
<td>.641</td>
</tr>
</tbody>
</table>

*Analysis obtained using 73 subjects.
†Analysis obtained using 43 subjects with visualized BAT.

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![Figure 1](image1.png)

**Figure 1. Bar graphs** showing the percentage of prepubertal (Tanner stage 1) and pubertal (Tanner stage 2-5) boys and girls depicting BAT. There is a statistically significant difference in the percentage of subjects depicting BAT between prepubertal (0%) and pubertal (67%) girls (**\( P = .005 \)) and between prepubertal (20%) and pubertal (87%) boys (**\( P < .0001 \)).

![Figure 2](image2.png)

**Figure 2.** A, Relationship between BAT volume and age in 43 boys and girls with visualized BAT (\( r = 0.77 \) for boys and \( r = 0.72 \) for girls; both \( P < .001 \)). B, Relationship between BAT volume and Tanner stage in 43 boys and girls with visualized BAT (\( r = 0.70 \) for boys and \( r = 0.54 \) for girls; both \( P \leq .01 \)).
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 2 tissues.

In humans, the greatest gains in skeletal muscle occur during the fetal stage, infancy, and puberty. Concurrently, all fetus and newborns have BAT, and as the results of the current imaging study strongly indicate, large amounts of BAT 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 identification of the factors responsible not only for the rapid increase in BAT that occurs during puberty, but also for sex differences in BAT. The recent development of noninvasive magnetic resonance imaging techniques to characterize BAT could add greatly to our understanding of the contributions of this important tissue in regulating human physiology.

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50 Years Ago in THE JOURNAL OF PEDIATRICS

A Review of Chromosome Studies in the Diagnosis of Mongolism—Case Report of a Chinese Infant
Conen PE, Bell AG, Rance CP. J Pediatr 1962;60:533-9

In 1962, the human karyotype had been established for 6 years.1 The cause of Down syndrome was known to be a third copy of chromosome 21 in most cases, with smaller numbers exhibiting translocations or mosaicism. Fifty years later, the karyotypic categories remain the same, although the technology permits identification of trisomies for portions of chromosome 21. Our vocabulary has changed dramatically: “Mongolism” is completely unacceptable. “People first” language is important; the identity of this individual does not equate with the medical diagnosis. This is “a child with Down syndrome.” The terms “mentally retarded,” “MR,” and “retarded” should be replaced by “intellectual and developmental disability” or “IDD,” because the school yard use of the “R-word” has led to a movement to ban its use entirely.2

The outcomes for people with Down syndrome have changed remarkably. In 1963, the average life expectancy for someone with Down syndrome was 18 years of age,3 but today it is approximately 60 years.4 The rise in the median age at death for individuals with Down syndrome from 25 years in 1983 to 49 years in 1997 has been suggested to be caused, at least in part, by access to cardiovascular surgery for babies born with Down syndrome and congenital heart disease,5,6 an intervention not available to a child with Down syndrome in 1962.

A child born with Down syndrome in 1962 would have had a high probability of being institutionalized, with the consequent risks to health and lack of stimulation. A child born in 2012 with Down syndrome should have access to life-saving surgeries, early educational intervention, mainstreaming, inclusion, and educational expectations. Respect for that child results in superior outcomes.

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References
Figure 3. Relationship between BAT volume and trunk muscle volume in 43 boys and girls with visualized BAT ($r = 0.52$ for boys and $r = 0.64$ for girls; both $P < .01$).