Functional Brown Adipose Tissue is Related to Muscle Volume in Children and Adolescents

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Abstract

Objective—We examined whether the depiction of brown adipose tissue (BAT) with positron emission tomography/computed tomography (PET/CT) in pediatric patients is associated with anthropometric meaures.

Study design—We determined measures of body mass, adiposity, and musculature in 71 children and adolescents who underwent PET/CT examinations and compared patients with and without BAT. We used regression analyses to assess the relation between BAT and anthropometric measures.

Results—A total of 30 patients (42%) had BAT depicted on PET/CT, 10 of 26 girls (38%) and 20 of 45 boys (44%). Compared with patients without functional BAT, patients with BAT had significantly greater neck musculature (1880 ± 908 cm^3 versus 1299 ± 806 cm^3; $P = .028$ for boys and 1295 ± 586 cm^3 versus 854 ± 392 cm^3; $P = .030$ for girls) and gluteus musculature (1359 ± 373 cm^3 versus 1061 ± 500 cm^3; $P = .032$ for boys and 1138 ± 425 cm^3 versus 827 ± 297 cm^3; $P = .038$ for girls), but no differences in age, body mass index, or measures of subcutaneous fat. With logistic regression analyses, neck and pelvic musculature predicted the presence of BAT independently of age, sex, body size, and season of scan ($P = .018$ and .009, respectively).

Conclusion—Pediatric patients with visualized BAT on PET/CT examinations had significantly greater muscle volume than patients with no visualized BAT.

The adipose organ is a complex endocrine system, composed of white and brown adipose tissue (BAT). White adipose tissue (WAT) 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] Rich in mitochondria, BAT generates heat through the uncoupling of oxidative respiration from the production of adenosine triphosphate, an action regulated by uncoupling protein-1, uniquely expressed in brown adipocytes.[4–6] All newborns have considerable amounts of BAT, and recent data with fluoro-deoxyglucose-based positron emission tomography/computed tomography (PET/CT) found significant amounts of metabolically active BAT in as many as 8% of adults.[1]

Adipose and musculoskeletal tissues originate from the mesoderm, and the prevailing model has been that a common stem cell gives rise to WAT, BAT, bone, and muscle.[7,8] In an

intermediate developmental step, it was assumed that WAT and BAT share a common precursor because both forms of adipose tissue express a similar array of genes involved in triglyceride metabolism.[9] However, although it is possible to convert WAT precursors into brown adipocyte-like cells,[10] evidence also suggests that brown adipocytes are developmentally close to skeletal muscle.[11–15] An in vivo study by Seale et al indicates that some brown fat cells arise from the same *Myf5*-expressing progenitor as skeletal muscle cells, whereas white fat cells do not.[11] Consistent with this notion are data indicating that brown adipocytes and skeletal muscle cells share many features: an abundance of mitochondria, energy expenditure via oxidative phosphorylation, and sympathetically mediated adaptive thermogenesis.[16,17] Moreover, brown adipocytes have been identified in skeletal muscle, and their abundance in different strains of mice correlates with differences in energy expenditure and protection against obesity.[18]

Studies in animals have shown that although reduced amounts or function of BAT lead to obesity, insulin resistance, and dyslipidemia,[19,20] increased amounts or function of BAT protect against obesity and its co-morbidities.[21–23] An inverse relation between body mass and body fat and the uptake of fluoro-deoxyglucose by BAT in PET examinations has also been suggested in humans.[1,6,24,25] Obese and overweight adults and elderly patients exhibit less BAT uptake than lean and younger subjects. On the basis of these data, modulation of BAT activity has been proposed as a potential strategy to combat obesity and its associated co-morbidities.[26–29]

In this study, we examine whether the depiction of BAT in children, adolescents, and young adult male and female patients undergoing PET/CT examination is related to their body mass, adiposity, or skeletal musculature.

Methods

The institutional review board for clinical investigations at Children's Hospital Los Angeles approved this retrospective study; informed consent was waived, and this study was compliant with the Health Insurance Portability and Accountability Act. The study population comprises 71 patients, aged 6 to 20 years old, 45 male and 26 female. Of the 71 patients, 56 had lymphoma (35 Hodgkin's, 3 Burkitt's, 8 B-cell, 3 anaplastic large cell, 7 lymphoma), 3 had neuroblastoma, 2 had Ewing's sarcoma, 2 had acute lymphoblastic leukemia, and 1 had each of the following: adenosarcoma, adenocarcinoma, angiosarcoma, melanoma, nasopharyngeal carcinoma, rhabdomyosarcoma, and carcinomas of the thyroid and liver. 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 values were corrected 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 2.2 and 12.9 mCuries, depending on body weight. Oral contrast medium (meglumine diatrizoate, Gastrografin, Bristol-Myers Squibb, New York, New York) was administered in all patients. No muscle relaxants or additional agents were administered, nor were any patients subjected to cold and warm temperature preparations. All patients were indoors in room temperature (22°C) for >2 hours before examination. However, because of a lack of co-operation, children <6 years of age underwent general anesthesia and were excluded from this study. In patients who underwent repeated examinations, only initial PET/CT studies were used for analyses.

All PET/CT studies were reviewed independently by two radiologists to determine the presence or absence of metabolically active BAT in the neck, supraclavicular, paravertebral, and pararenal areas. A patient was considered to have BAT when both radiologists diagnosed its presence. Studies with discrepant determinations were re-evaluated by both radiologists together to arrive at a consensus.

Muscle and fat tissue volumes were measured semi-quantitatively on the basis of CT Hounsfield units (HU). In brief, the volume of neck adiposity was assessed by calculating all negative HU voxels[30] (after manually excluding the airway), and the volume of cervical musculature was determined by calculating all positive HU voxels[31] (after manually excluding the thyroid, bone, lymph nodes, and vessels) from the first cervical vertebrae to the upper portion of the sternum. The volume of gluteal musculature was determined by measuring all voxels with positive HU values (excluding bone) behind the ileac bones, from the ileac crest to the femoral heads. The volumes of subcutaneous fat in the buttocks were measured from the same scans by measuring all voxels with negative HU values adjacent to the gluteus muscles. All analyses were done with a workstation (Philips Extended Brilliance Workspace, Cleveland, Ohio) and Matlab (The Mathworks, Natick, Massachusetts).

Statistical analysis was carried out with Statview software (version 5.0.1; SAS Institute, Cary, North Carolina) by using the *t* test for unpaired samples and logistic linear regression analyses. Presence or absence of BAT was used as the outcome variable, and age, sex, BMI, season (defined as spring, summer, fall, or winter), and musculature were used as independent variables. In building the model, we included BMI to adjust for the confounding effects of body size, but excluded weight, height, and measures of subcutaneous adiposity to avoid multicollinearity in co-variates. All values are expressed as means plus or minus SD.

Results

A total of 30 of the 71 examinations (42%) depicted BAT. Visualized active BAT had standard uptake values ranging from 1.41 to 3.94 standard uptake values max. There were no significant sex differences in the prevalence of BAT (10 of 26 for female patients versus 20 of 45 for male patients; *P* = .63). Table I describes the age, anthropometric characteristics, and neck and buttock adiposity and musculature in BAT +/− studies for male and female patients. Male patients with BAT were taller than male patients without BAT (*P* = .034). In contrast, the heights of female patients with or without BAT were similar, and there were no differences in the age, weight, BMI, and measures of adiposity in the neck or buttocks of patients with and without BAT (all *P* values >.05), regardless of sex.

The Figure shows box plots for measures of cervical and gluteal muscle volumes for male and female patients. Regardless of sex or anatomical site, there were significant differences in muscle volume between patients with and patients without functional BAT. For all comparisons, the upper 50th percentile of values for muscle in patients with BAT was >75th percentile of the measures in patients without BAT.

Table II shows the correlations among age, anthropometric measures, and values for adiposity and musculature in male and female patients. Regardless of sex, there were significant correlations seen between BAT +/− and neck and gluteus musculature (r values between 0.32 and 0.43; all *P* values between .028 and .037). In contrast, neither age, weight, height, BMI, or neck or buttock fat were associated with the presence or absence of BAT (Table II). Multiple logistic regression analyses indicated that both appendicular and axial musculature were independently associated with the presence of BAT, after accounting for age, sex, BMI, and season (Table III).

Discussion

In this study, we found that young patients with functioning BAT on PET/CT examinations had significantly greater muscle volume than patients of the same age and BMI with no visibly identifiable BAT. These findings were present in the axial and appendicular skeletons of both male and female patients. On average, patients with pediatric cancer who had visualized BAT had 50% greater neck volume and 33% greater gluteal muscle volume than patients with no BAT. Additionally, we found significant relations between the presence of BAT and the volume of muscle in the axial and appendicular skeletons, which were independent of age, sex, body size, and season in which the study was done. Our results showing a link between BAT and muscle in patients undergoing PET/CT examinations represent the clinical correlate of basic studies indicating that brown fat and skeletal muscle share a common progenitor cell.[11]

In contrast, the results of this study show no significant differences in the age, weight, BMI, or measures of subcutaneous adiposity between patients with and patients without functioning BAT. Earlier studies on the relation among BAT and BMI and adiposity were generally done in adult populations and yielded conflicting results. Although some studies found inverse relations between BAT and BMI, between BAT and measures of adiposity, or both,[1,6,24,25] other studies found no such relation.[2,32–34] These discrepant results may be caused by differences in patient populations and in measurement instruments. Generally, the relations between BAT and adiposity were analyzed solely with anthropometric measurements and less frequently with bioelectric impedance[2,34] or dual-energy absorptiometry[24] in studies with small cohorts. The use of CT, an imaging modality that provides accurate and independent measurements of muscle and adipose tissue simultaneously in a relatively large number of patients, is a strength of this study.

Our study corroborates earlier investigations suggesting a higher prevalence of BAT in pediatric PET/CT studies[35–37] when compared with that reported for adult patients.[1] It also indicates that the presence of BAT is common in PET/CT examinations of children and adolescents, even when they live in warm climates like California. This was somewhat unexpected, because BAT activity is greater in colder climates, consistent with the need for non-shivering thermo-genesis.[38] Moreover, earlier data suggest that nearly all PET/CT examinations in young men depict BAT when obtained at 16°C,[24] half when measured at 19°C,[2,34] but none when examinations were obtained during warmer conditions. However, we found that approximately 40% of PET/CT studies in young patients from our study cohort depicted BAT, even when obtained under thermoneutral conditions (22°C).

This study has several notable limitations. It is based on a retrospective, cross-sectional analysis of PET/CT examinations of children and adolescents with cancer. Further work is needed to investigate and better determine the strength of this association in the elderly and in healthy populations. Most important, information on the total amount of BAT is unavailable, and it is likely that depicted metabolically active BAT represents only a small, undetermined proportion of total BAT. Indeed, whether the association found between functional BAT in the upper body and gluteal musculature is a result of the strong correlation between nuchal and gluteal musculature, the surrogacy of functional BAT as a measure of brown fat at other anatomical sites, or a distant effect is unknown. However, finding an association between BAT and muscle in patients with significant disease and with a technique that does not allow for the complete characterization of BAT underscores the strength of the link between these two tissues. The recent development of sensitive and noninvasive magnetic resonance imaging techniques to characterize BAT could greatly aid in delineating the contributions of this tissue in regulating human physiology.[39]

Glossary

BAT	Brown adipose tissue
BMI	Body mass index
HU	Hounsfield units
PET/CT	Positron emission tomography/computed tomography
WAT	White adipose tissue

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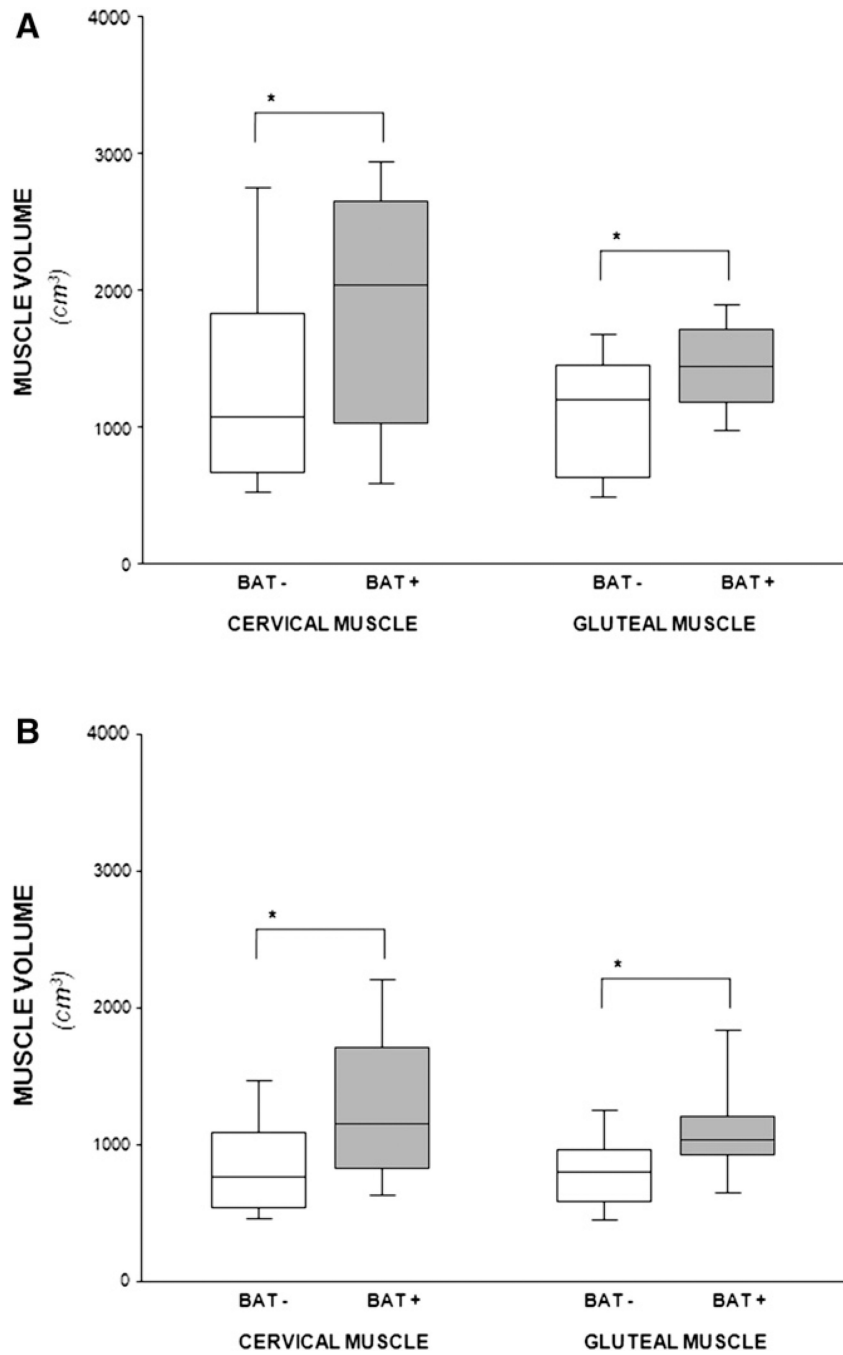
Figure.
Box plot of cervical and gluteal muscle volume comparing patients with and without visualized BAT. **A,** Male patients; **B,** Female patients. *P < .04.

Table I

Age, anthropometric measures, and measures of muscle and fat in brown adipose tissue-positive and −negative male and female patients

	Male patients			Female patients		
	BAT+ (n = 20)	BAT− (n = 25)	P value	BAT+ (n = 10)	BAT− (n = 16)	P value
Age, years	15.0 ± 3.5	13.5 ± 3.9	.187	14.9 ± 3.5	13.9 ± 4.2	.532
Weight, kg	64.1 ± 19.6	52.0 ± 24.8	.082	61.2 ± 26.8	49.0 ± 19.4	.190
Height, cm	165 ± 20	152 ± 21	.034	157 ± 13	149 ± 12	.138
BMI	22.9 ± 4.0	21.6 ± 6.8	.443	24.6 ± 10.5	21.5 ± 6.3	.365
Neck fat, cm^3	544 ± 443	513 ± 707	.867	835 ± 836	514 ± 500	.230
Buttock fat, cm^3	799 ± 449	867 ± 636	.686	1120 ± 883	823 ± 775	.377
Neck muscle, cm^3	1880 ± 908	1299 ± 806	.028	1295 ± 586	854 ± 392	.030
Gluteus muscle, cm^3	1359 ± 373	1061 ± 500	.032	1138 ± 425	827 ± 297	.038

Table II

Simple correlations of age, anthropometric measures, and measures of fat and muscle in male and female patients

	Age	Weight	Height	BMI	Neck fat	Buttock fat	Neck muscle	Gluteus muscle	BAT +/−
Age	1.00	0.74*	0.86*	0.38*	0.28	0.11	0.82*	0.77*	0.20
Weight	0.63*	1.00	0.79*	0.82*	0.66*	0.42*	0.83*	0.88*	0.26
Height	0.73*	0.60*	1.00	0.34*	0.21	0.17	0.78*	0.81*	0.32
BMI	0.44*	0.93*	0.27	1.00	0.85*	0.54*	0.56*	0.61*	0.12
Neck fat	0.50*	0.90*	0.36	0.92*	1.00	0.53*	0.42	0.41*	0.03
Buttock fat	0.37	0.86*	0.28	0.90*	0.77*	1.00	0.25	0.24	−0.06
Neck muscle	0.45*	0.79*	0.52*	0.69*	0.77*	0.56*	1.00	0.86*	0.34*
Gluteus muscle	0.57*	0.91*	0.53*	0.86*	0.80*	0.79*	0.75*	1.00	0.32*
BAT +/−	0.13	0.27	0.30	0.19	0.24	0.18	0.43*	0.41*	1.00
						Female patients (n = 26)		Male patients (n = 45)	

Male patients (n = 45) and female patients (n = 26).

*
All *P* values <.05.

Table III

Multiple logistic regression models for the prediction of brown adipose tissue

	β	SE	*P* value	R^2
BAT ±				
Age	−0.084	0.102	.406	
Sex	0.487	0.604	.420	
BMI	−0.020	0.047	.670	0.103
Season	0.123	0.238	.607	
Neck muscle	0.001	0.001	.018	
BAT ±				
Age	−0.114	0.107	.284	
Sex	0.639	0.635	.314	
BMI	−0.075	0.059	.205	0.124
Season	0.123	0.243	.612	
Gluteus muscle	0.003	0.026	.010	