Published in final edited form as:

Obesity (Silver Spring). 2020 February ; 28(2): 241–246. doi:10.1002/oby.22698.

Sexual Dimorphisms in Adult Human Brown Adipose Tissue

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Abstract

Objective—To quantify and compare the amount, activity, and anatomical distribution of cold-activated brown adipose tissue (BAT) in healthy, young, lean women and men.

Methods—BAT volume and ¹⁸F-fluorodeoxyglucose uptake was measured by positron emission tomography/computerized tomography (PET/CT) in 12 women and 12 men (BMI 18.5–25 kg/m², ages 18–35), after 5 hours of exposure to their coldest temperature before overt shivering.

Results—Women had lower detectable BAT volume than men (p=0.03), but there was no difference after normalizing to body size. Mean BAT glucose uptake and relative distribution of BAT did not differ by sex. ¹⁸F-fluorodeoxyglucose uptake consistent with BAT was observed in superficial dorsocervical adipose tissue of 6/12 women but only 1/12 men (p=0.02). This potential BAT depot would pose fewer biopsy risks than other depots.

Conclusions—Despite differences in adiposity and total BAT volume, we found that healthy, lean, young women and men do not differ in the relative amount, glucose uptake, and distribution of BAT. Dorsocervical ¹⁸F-fluorodeoxyglucose uptake was more prevalent in women and may be a remnant of interscapular BAT seen in human newborns. Future studies are needed to discern how BAT contributes to whole-body thermal physiology and body weight regulation in women and men.

Keywords

Imaging; Brown Adipose Tissue; Body Fat Distribution

Introduction

Obesity results from caloric intake exceeding expenditure. White adipose tissue (WAT) stores surplus energy. Brown adipose tissue (BAT) expends energy as heat (1) after cold- or

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DISCLOSURE: The authors declare no conflict of interest.

CLINICAL TRIAL REGISTRATION:

pharmacologic-stimulation (2, 3) and is a therapeutic target for treating obesity and metabolic disease.

Most prospective studies of human BAT were conducted on males (4), yet many adipose-related sexual dimorphisms exist. Women tend to have proportionally more total body fat (5), greater subcutaneous fat, but less visceral fat (6) than men. Despite these observations, quantitative BAT differences based on sex have been largely unstudied. Here we determined whether women and men have different amount, activity, or anatomical distribution of BAT.

Methods

Protocol Design.

Twenty-four young (18–35y), lean (BMI 18.5–25 kg/m²), healthy female and male volunteers (12 each) were admitted to the National Institutes of Health Clinical Center for a continuous 7–13-day inpatient protocol approved by the Institutional Review Board (Clinical Trial Identifier:) and described previously (7, 8). All were nonsmokers, had no metabolic or psychological conditions, and took no medication except oral contraceptives for women. Women were measured in the follicular phase. Subjects provided written informed consent.

Subjects wore sleeveless shirts, shorts, and light socks with combined thermal insulation of 0.34 clo. Women additionally wore a sports bra (+0.01 clo). Skin temperature of the left deltoid, pectoralis major, anterior thigh, and shin was measured via wireless thermistor probes (iButton, Maxim Inc.) and weighted mean skin temperature is reported (9). From 0800–1300, fasted subjects were exposed to a constant ambient air temperature between 16.0 and 31.0°C which differed each day in randomized order. Shivering was assessed via visual-analog-scale, participant-report, and direct observation. On the final day, subjects were re-exposed to their coldest temperature before overt shivering preceding BAT imaging by ¹⁸F-fluorodeoxyglucose positron emission tomography and computed tomography (¹⁸F-FDG PET/CT). Subjects were dosed with 370 MBq of ¹⁸F-FDG by i.v. injection at 1200, remained in the cold until 1300, and were scanned at ~1330 using four 5-minute-long bed-positions on a Siemens Biograph mCT (Siemens Healthcare).

Body Composition.

Body composition was measured by dual-energy X-ray absorptiometry (DXA; Lunar iDXA, GE Healthcare).

PET/CT Image Analyses.

We created regions-of-interest on each 3.5-mm axial slice of the PET/CT images in ImageJ as previously described (8, 10). We then applied a previously established CT Hounsfield Unit threshold (–300 to –10) and an individualized PET threshold normalized to lean body mass/total body mass ratio (8) to define active BAT voxels, after verifying mean ¹⁸F-FDG standardized uptake values (SUVs) of three reference tissues (deltoid muscle, liver, and cerebellum) were similar between men and women after applying this normalization (data not shown). Voxels identified as BAT in each region-of-interest were used to calculate total body BAT volume, SUVmean, and activity (BAT volume × SUVmean) (11).

Brown Adipose Tissue Quantification.

BAT distribution was categorized by six anatomical depots: cervical, supraclavicular, axillary, paraspinal, mediastinal, and abdominal, as previously described (8, 10). For this study, we used the PET/CT-based image analysis criteria described above to define potential BAT in a manner consistent with the BAT-reporting consensus statement (12) in an additional depot in the subcutaneous fat on the dorsal side of the cervical spine and refer to it as superficial dorsocervical BAT (sdBAT).

Statistical Analyses.

Statistical tests were performed in SAS JMP 14.0.0. Anthropometry and BAT were compared by sex with independent sample *t*-tests. Normalization of BAT volume to anthropometric variables was performed by dividing BAT volume by each variable. BAT volume in each depot was compared by sex using analysis of covariance controlling for total BAT volume and multiple comparisons. Correlations between sdBAT and total BAT volume were assessed with Spearman's rho (ρ). Prevalence of sdBAT by sex was compared via chi-square test. Results are median $\pm$ interquartile-range unless otherwise specified. P-values 0.05 were considered significant.

Results

Demographics.

Women were older and had higher body fat percentage and less lean mass than men. Neither ambient temperature ($20.7 \pm 1.5^\circ\text{C}$ vs. $21.6 \pm 2.4^\circ\text{C}$) nor skin temperature ($30.3 \pm 0.9^\circ\text{C}$ vs. $30.1 \pm 1.3^\circ\text{C}$) were different on scan day (Table 1).

BAT Volume and Activity.

Women had less detectable active BAT volume than men (179.4 ± 230.6 mL vs. 404.8 ± 202.3 mL, $p=0.03$) (Figure 1A), which persisted after normalizing to fat mass. However, there was no sex difference in BAT volume after normalizing to lean body mass, total body mass, or body surface area. BAT SUVmean, which reflects the concentration of tracer taken up in the region-of-interest relative to injection dose, was similar among females and males. Women and men also had similar total BAT ^{18}F -FDG uptake, reflecting similar overall BAT metabolic activity (900.6 ± 1190.0 vs. 2147.2 ± 1900.8 , $p=0.08$).

BAT Distribution.

The sex difference in BAT volume came primarily from the supraclavicular and paraspinal depots; men had significantly more active BAT in only these depots (Figure 1B). After adjusting for total active BAT volume, women and men had similar relative BAT distributions (Figure 1C–D).

Superficial Dorsocervical Depot.

Although continuous with the classical intermuscular cervical BAT depot via a thin fascial layer, a distinct, superficial adipose depot with ^{18}F -FDG uptake consistent with BAT was

identified on the dorsal side of the cervical spine in 6/12 women but only 1/12 men ($p=0.02$; Figure 2A).

In women, sdBAT volume and ^{18}F -FDG uptake correlated with total BAT volume and ^{18}F -FDG uptake, respectively (both p 's=0.03; Figure 2B and not shown). However, in women who had sdBAT, it accounted for only 1% of total BAT volume. Neither total BAT nor sdBAT volumes correlated with ambient temperature on scan day (Figure 2C) or glucose uptake in reference tissues (data not shown) in men or women.

Discussion

Sexual dimorphisms in human adiposity have been long established, yet little is known about BAT differences between men and women. In retrospective studies of thousands of patients undergoing PET/CT, BAT FDG-uptake is consistently found more frequently in women than men (11, 13). However, in controlled cohort studies, there has not been an apparent dimorphism (14). Here, a more nuanced story emerged: during cold exposure, women had less active BAT volume than men, but when normalized to total body mass or BSA, this difference did not persist. This indicates that differences in absolute BAT volume may be due to body size differences between sexes. In terms of either mean or total metabolic activity, BAT glucose uptake was comparable between men and women.

By anatomical depot, women and men have similar BAT distributions. However, a sexual dimorphism does exist in the presence of what we have termed sdBAT. Heaton first recognized histological evidence for BAT in the “subcutaneous interscapular area” in adult autopsies, but did not comment on depot-specific sexual dimorphisms (15). In our study, half the women, but only one man had potential BAT in this depot, consistent with other reports (16, 17). In particular, Martinez-Tellez, et al. identified dorsocervical adipose tissue ^{18}F -FDG uptake in 23 of 133 young subjects, nearly all women ($n=22$). Our analysis now provides quantification of this region as it relates to full-body BAT (16). Although sdBAT accounts for <1% of total BAT in those who have it and we have not observed a clear hierarchical cold-stimulated response pattern of BAT glucose uptake by depot, sdBAT volume and ^{18}F -FDG uptake correlate with total BAT volume and ^{18}F -FDG uptake, suggesting women with greater total BAT volume are more likely to present sdBAT.

Based on its location, we hypothesize sdBAT is a remnant of interscapular BAT seen in human newborns (18) and a homolog of the principal functional BAT depot in rodents (1). However, because this depot may be susceptible to imaging artefacts such as compression and partial volume effects, future studies must confirm whether sdBAT performs thermogenesis in vivo and contains BAT biomolecular markers. It is imperative to understand the functional role of sdBAT, why an apparent involution of this depot occurs, and why it is more prevalent in females than males. Practically, procuring biopsy tissue from this region should involve less patient risk than other BAT depots as it has fewer proximate nerves and major blood vessels and is the most superficial depot identified thus far (19).

This study has several limitations. We used ^{18}F -FDG uptake for BAT quantification, which does not account for fatty acid consumption (20). Repeated cold exposures can increase BAT

^{18}F -FDG uptake (20). We mitigated this effect by randomizing ambient temperature order. It is unknown if men and women have comparable adipocyte heterogeneity in fat depots. Finally, this study only included healthy, lean, young subjects.

In summary, despite differences in adiposity and total BAT volume, healthy, lean, young women and men do not differ in relative amount, glucose uptake, and distribution of BAT. Sexual dimorphisms do exist though—sBAT is more prevalent in women than men. Based on its anatomy, we hypothesize sBAT is a remnant of interscapular BAT seen in human newborns. Our findings highlight the need to further investigate how BAT contributes to whole-body thermal physiology and body weight regulation in women and men.

Acknowledgements

We thank study participants, Metabolic Clinical Research Unit nurses and nutrition team, NIH PET/CT Department for administering scans, Ilan Tal for software development, and Sungyoung Auh for statistical assistance. Deidentified data is available upon request.

FUNDING: NIDDK Intramural Funding Z01 DK071014 (K.Y.C.) and DK075116–02 (A.M.C.).

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What is already known about this subject?

- BAT expends energy in the form of heat and is therefore a potential target for therapeutic interventions to address obesity and metabolic disease
- Sexual dimorphisms exist in terms of general adiposity and metabolism
- Most BAT studies are conducted in rodents; most quantitative clinical trials of human BAT have been conducted in men

What does your study add?

- A quantitative analysis of cold-induced BAT in healthy, lean, young women and men to explore the differences in amount, activity, and anatomical distribution
- Women had less BAT volume than men, but the relative amount, metabolic activity, and distribution of detectable BAT were similar
- Superficial dorsocervical adipose tissue with BAT-like glucose uptake was more prevalent in women, and is a probable remnant of interscapular BAT seen in rodents and human newborns

Figure 1.

Distribution of human BAT in male (solid) and female (striped) subjects. (A) Total active BAT (mean $\pm$ SD) in 12 male subjects and 12 female subjects. (B) Average (SD) amount of active BAT in the defined anatomic depots. (C) Representative regional distribution of BAT in the defined anatomic depots. On the left, 18 y.o. male, BMI 22.3; on the right, 31 y.o. female, BMI 24.6. (D) Relative BAT distribution as average percentage of total BAT volume. $P > 0.05$ for all depots. In B, superficial dorsocervical depot is represented in cervical depot bars. $*P < 0.05$.

Figure 2.

Superficial dorsocervical BAT. (A) Intermuscular cervical versus superficial dorsocervical BAT (sdBAT) in a male subject (left) and female subject (right). The subjects are the same as in Figure 1C. (B) Correlation between sdBAT volume and total BAT volume in male subjects (left) and female subjects (right). (C) Total BAT volume versus scan day ambient temperature (left) and sdBAT volume versus scan day ambient temperature (right). In B and C, closed squares and dots represent males and females without sdBAT; open squares and dots represent males and females with sdBAT.

Table 1.

Subject Demographics.

	Male (n=12)	Female (n=12)	P value
Characteristics and Body Composition			
Age (y)	22.5 ± 4.9	27.8 ± 3.6	0.01
Weight (kg)	77.8 ± 8.8	61.4 ± 8.8	<0.001
Height (cm)	183.0 ± 7.0	166.8 ± 7.0	<0.001
BMI (kg/m ²)	23.2 ± 1.9	22.0 ± 2.5	0.22
Fat Mass (kg)	16.2 ± 5.5	19.8 ± 6.2	0.13
% Fat	20.6 ± 5.7	31.8 ± 6.6	<0.001
Lean Mass (kg)	57.8 ± 6.3	40.0 ± 4.4	<0.001
Scan Day Conditions			
Ambient Temperature (°C)	21.2 ± 1.5	20.3 ± 1.3	0.12
Weighted Mean Skin Temperature (°C)	29.8 ± 0.8	30.3 ± 0.5	0.13
Individualized BAT SUV Threshold for PET Image Analysis	1.6 ± 0.1	1.9 ± 0.2	<0.001
BAT Volume (mL)			
Total	334.0 ± 187.6	194.3 ± 95.1	0.03
Superficial Dorsocervical	0.5 ± 1.9	1.8 ± 3.4	0.27
Cervical	42.3 ± 30.6	27.7 ± 18.0	0.17
Supraclavicular	119.6 ± 66.8	60.5 ± 38.7	0.01
Mediastinal	15.6 ± 17.0	7.0 ± 9.2	0.14
Axillary	22.6 ± 15.7	20.0 ± 18.5	0.71
Paraspinal	93.9 ± 53.7	51.8 ± 25.7	0.02
Abdominal	45.5 ± 43.3	21.5 ± 14.3	0.08
BAT SUVmean			
Total	4.91 ± 1.64	5.01 ± 1.51	0.88
Superficial Dorsocervical *	2.4	3.0 ± 0.9	NA
Cervical	5.8 ± 2.5	6.0 ± 2.3	0.86
Supraclavicular	5.4 ± 1.8	5.4 ± 2.0	0.97
Mediastinal	3.7 ± 1.0	3.3 ± 1.0	0.40
Axillary	3.6 ± 1.0	3.5 ± 1.1	0.77
Paraspinal	4.6 ± 1.9	5.3 ± 1.8	0.35
Abdominal	4.5 ± 1.4	3.5 ± 0.9	0.06
BAT Activity (¹⁸F-FDG uptake)			
Total	1890.8 ± 1277.8	1094.2 ± 765.0	0.08
Superficial Dorsocervical	1.3 ± 4.6	6.6 ± 14.0	0.23
Cervical	291.0 ± 259.6	187.6 ± 170.6	0.26
Supraclavicular	730.4 ± 471.3	389.6 ± 329.8	0.052
Mediastinal	64.0 ± 69.7	29.3 ± 43.9	0.16

	Male (n=12)	Female (n=12)	P value
Axillary	91.2 ± 77.7	83.7 ± 86.9	0.83
Paraspinal	498.7 ± 355.8	292.8 ± 207.8	0.10
Abdominal	236.4 ± 258.3	83.7 ± 62.2	0.06
BAT Radiodensity from CT (HU)			
Total	-45.1 ± 6.8	-43.1 ± 10.2	0.79
Superficial Dorsocervical *	-46.5	-57.3 ± 10.5	NA
Cervical	-15.5 ± 12.9	-40.5 ± 14.6	0.005
Supraclavicular	-41.5 ± 14.5	-52.1 ± 10.4	0.12
Mediastinal	-61.4 ± 19.0	-41.6 ± 20.4	0.07
Axillary	-47.7 ± 20.6	-52.5 ± 14.7	0.78
Paraspinal	-49.2 ± 15.6	-35.8 ± 10.0	0.03
Abdominal	-60.9 ± 31.0	-37.6 ± 12.0	0.07

All values are mean ± standard deviation,

* averages from 1 male participant and 6 female participants with superficial dorsocervical BAT