Wien Klin Wochenschr (2013) 125:687–695
DOI 10.1007/s00508-013-0431-2

Wiener klinische Wochenschrift
The Central European Journal of Medicine

Differences in the metabolic status of healthy adults with and without active brown adipose tissue

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Received: 1 May 2013 / Accepted: 13 September 2013 / Published online: 22 October 2013

Summary
Background Previous studies have proven the existence of active brown adipose tissue (BAT) in adults; however, its effect on systematic metabolism remains unclear.

Aim The current study was designed to investigate the differences in the metabolic profiles of healthy adults with and without active BAT using positron emission tomography–computed tomography (PET-CT) scans in the un-stimulated state.

Methods A cross-sectional analysis was performed to assess the health of adults using PET-CT whole-body scans at Huashan Hospital Medical Centre between November 2009 and May 2010. A total of 62 healthy adults with active BAT were enrolled in the BAT-positive group. For each positive subject, a same-gender individual who underwent PET-CT the same day and who had no detectable BAT was chosen as the negative control. Body composition was measured, and blood samples were collected for assays of metabolic profiles and other biomarkers.

Results In both the male and female groups, BAT-positive individuals were younger and had lower body mass indexes, fasting insulin, insulin resistance, and leptin, but a greater level of high-density lipoprotein cholesterol compared with the negative controls. In the male group, body fat content and levels of tumor necrosis factor-α were significantly lower in the BAT-positive than in the negative control group.

Conclusions The healthy adults with active BAT in an un-stimulated state had favorable metabolic profiles suggesting that active BAT may be a potential target for preventing and treating obesity and other metabolic disorders.

Keywords Brown adipose tissue · Human · Metabolism · High-density lipoprotein cholesterol

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Unterschiede im Stoffwechselstatus gesunder Erwachsener mit und ohne aktivem braunem Fettgewebe

Zusammenfassung
Grundlagen Frühere Studien haben die Existenz von aktivem braunem Fettgewebe (BAT) bei Erwachsenen nachgewiesen. Die Wirkung dieses Gewebes auf den systemischen Stoffwechsel bleibt allerdings unklar.

Ziel Die vorliegende Studie plante zu erforschen, ob ein Unterschied in den Stoffwechselprofilen gesunder Erwachsener mit beziehungsweise ohne BAT besteht, wobei PET-CT Scans im nicht stimulierten Zustand verwendet wurden.

Methodik Am Huashan Hospital Medical Center wurde zwischen November 2009 und Mai 2010 eine horizontale Analyse durchgeführt, um die Gesundheit von

Erwachsenen zu erfassen, wobei PET-CT Ganzkörper Scans zur Verwendung gelangten. Insgesamt wurden 62 gesunde Erwachsene mit aktivem BAT in die BAT positive Gruppe aufgenommen. Für jede positiv getestete Person wurde als negative Kontrolle eine Person gleichen Geschlechts ausgewählt, die am selben Tag eine PET-CT Untersuchung hatte und bei der kein aktives BAT nachgewiesen werden konnte. Die Körperzusammensetzung wurde gemessen und Blutproben zur Bestimmung von Stoffwechselprofilen und anderer Bio-Marker wurden abgenommen.

Ergebnisse Sowohl die männlichen als auch die weiblichen BAT positiven Individuen waren jünger und hatten einen geringeren BMI, ein niedrigeres Nüchtern-Insulin, niedrigere Insulinresistenz und Leptin. Nur das HDL-Cholesterin war im Vergleich zur BAT negativen Gruppe erhöht. Bei den BAT positiven Männern war der Körperfettgehalt und die Konzentration von Tumornekrosefaktor-alpha (TNF alpha) signifikant niedriger als bei den BAT negativen Kontrollen.

Schlussfolgerungen Die gesunden Erwachsenen mit aktivem BAT hatten im nicht-stimulierten Zustand ein günstigeres Stoffwechselprofil. Dies legt nahe, dass das aktive BAT ein mögliches Zielorgan bei der Vorbeugung und Behandlung der Adipositas und anderer Stoffwechselerkrankungen sein könnte.

Schlüsselwörter Braunes Fettgewebe (BAT) · Humaner Metabolismus · Stoffwechselprofil · HDL-Cholesterin

Abbreviations

BAT	Brown adipose tissue
PET-CT	Positron emission tomography–computed tomography
BMI	Body mass index
HDL-c	High-density lipoprotein cholesterol
LDL-c	Low-density lipoprotein cholesterol
TNF-α	Tumor necrosis factor-α
SUV	Standard uptake value
FDG	Fluorodeoxyglucose
WHR	Waist–hip ratio
HOMA-IR	Homeostatic model of assessment—insulin resistance
FABP4	Free fatty acid-binding protein-4
UCP1	Uncoupling protein 1
MET	Metabolic equivalent

Introduction

Brown adipose tissue (BAT) plays an important role in the thermogenesis and homeostasis of energy metabolism [1]. Active BAT, with a high standard uptake value (SUV), has been shown by positron emission tomography–computed tomography (PET-CT) scans in adults, confirmed by biopsy, and proven by several independent studies [2–4]. In the un-stimulated state, the general prevalence of BAT detected by PET-CT varies from 2.5 –8 %, but can be increased to approximately 95.8 % (23 of 24) when triggered by cold stress (16 °C) for 2 h [2]. In addition, the uptake of fluorodeoxyglucose (FDG) by BAT can be inhibited by heat, special medicines such as propranolol, or a high-fat diet [5, 6]. Retrospective studies, based mainly on patients with tumors, have shown that the probability of the detection of BAT is inversely correlated with age, outdoor temperature, and body mass index (BMI) [3]. In 2009, Saito et al. [7] found that the amount of BAT quantified in the neck area was inversely correlated with BMI and fat mass. In 2009, Van Marken Lichtenbelt et al. [2] also found that BAT activity under cold stress was negatively correlated with the percentage of body fat and positively correlated with resting metabolic rate. These results suggested that active BAT in adults may be beneficial to systemic metabolism, and that triggering BAT activity or enhancing the formation of BAT might be another useful strategy for fighting obesity and obesity-related disorders. However, the potential differences in the metabolic profiles of healthy adults with and without active BAT in an un-stimulated state have not been investigated.

In this cross-sectional study, the differences of systemic metabolic profiles were compared between healthy adults with and without active BAT detected by PET-CT in un-stimulated state.

Methods

Research design and procedure

In China, some individuals undergo PET-CT scan in some clinic centers to screen for tumor for health assessment. In this article, these healthy adults were recruited into the cross-sectional analysis just for health assessment in the medical examination center (PET-CT center in Huashan Hospital) at their own expenses, who also volunteered for scientific study and signed written consents between November 2009 and May 2010. All subjects were ≥18 years of age; had no history of obesity, diabetes, heart disease, severe infection, chronic liver or kidney disease, or cancer; and did not take any regular medications. Procedure of the study is shown in Fig. 1.

A total of 62 adults with active BAT, detected by PET-CT scan, were recruited as the BAT-positive group. For each BAT-positive subject, a negative control subject was chosen. To minimize possible interferences such as due to age, gender, or outdoor temperature, the negative control subject was of the same gender, was of the closest age possible to the positive individual, and underwent the scans on the same day. The ethics committee of Huashan Hospital at Fudan University approved the study, and written consent was obtained from all volunteers. The trial was registered at ClinicalTrials.gov (NCT01387438).

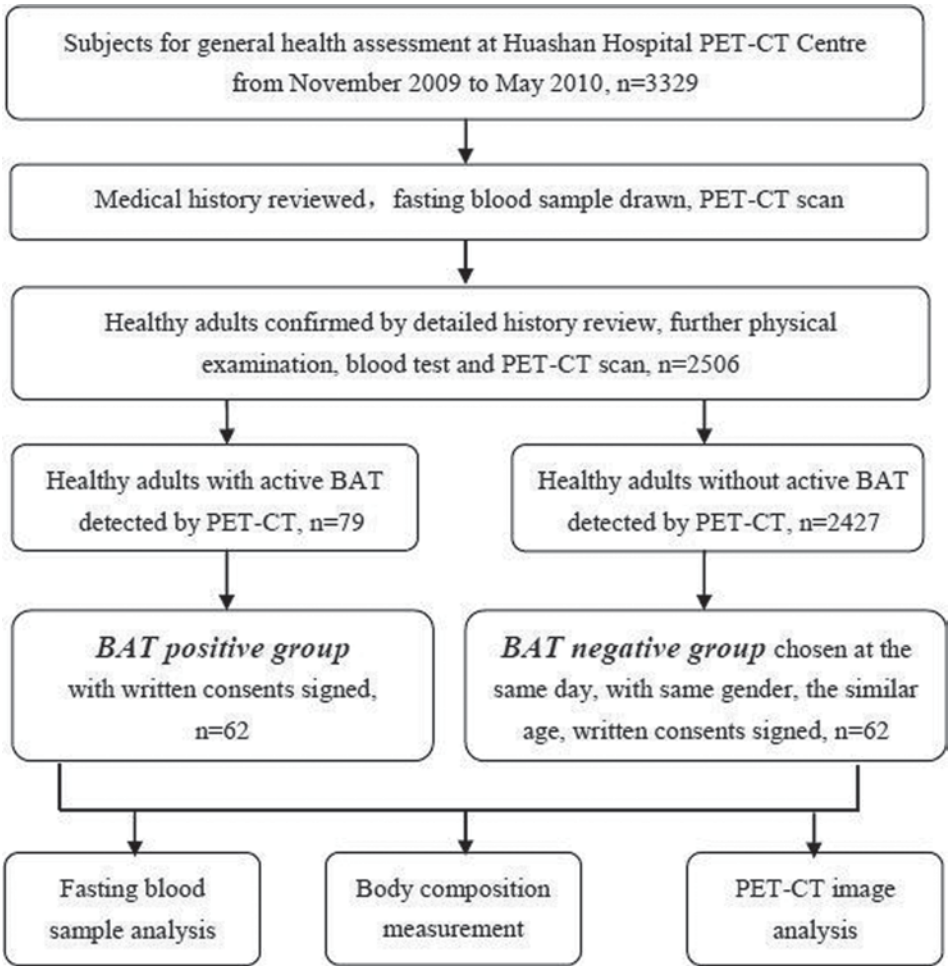

Fig. 1 Research design and procedure

PET-CT scan

In this study, the quantification of the activity of BAT in regions of interest, which included the principal cervical, supraclavicular, paravertebral, axillary, and superior mediastinal depots of BAT, was performed. Room temperature in the PET-CT center (31°12′ N, 121°30′ E) was maintained at 21–23°C. All subjects stayed in the room at least for 1 h before the injection of [^{18}F]FDG at a dose of 5.55–7.40 MBq/kg through the cubital vein, and they underwent PET-CT scan only one time. One hour after the injection, the whole-body images were acquired with Biograph 64 PET-CT scanners (SIEMENS, Germany). The CT scan time for the body was 2 min per bed position. Five or six bed positions per subject were needed to cover the areas where BAT is usually found. The resulting total average dose of radiation from the low-dose CT scan and the injected radioactive tracer was approximately 10.5 mCi. Calculations were completed with OpenPACS and PET-CT Viewer software (http://www.med.harvard.edu/JPNM/DisplayFreeware/) [8]. The adipose tissue was identified by CT (−250 to −50 Hounsfield units), and PET determined the uptake of [^{18}F]FDG. Areas of adipose tissue larger than 4 mm in diameter and with the maximum [^{18}F]FDG SUV (SUV max) of ≥2.0 were identified as the active BAT regions [3]. The example of two PET-CT images of subjects with and without active BAT is shown in Fig. 2.

Other data collection

Medical, smoking, and drinking histories, as well as exercise habits, height, weight, heart rate, and systolic blood pressure (SBP)/diastolic blood pressure (DBP), were collected from subjects before scanning, by the standard operation protocol. According to the type, the weekly frequency, and the duration of physical activities, the level of exercise was quantified synthetically. The level of exercise was classified by the respective metabolic equivalent (MET) value ("Yes" represented moderate or vigorous intensity of exercise ≥3 METs, "No" represented light intensity of exercise <3 METs) [9, 10]. Total percentage of fat content was measured via the body composition analyzer (TANITA, TBF-300A, Japan). Waist circumference was measured at the minimum circumference between the iliac crest and the rib cage, and hip circumference was measured around the maximum protuberance of the buttocks.

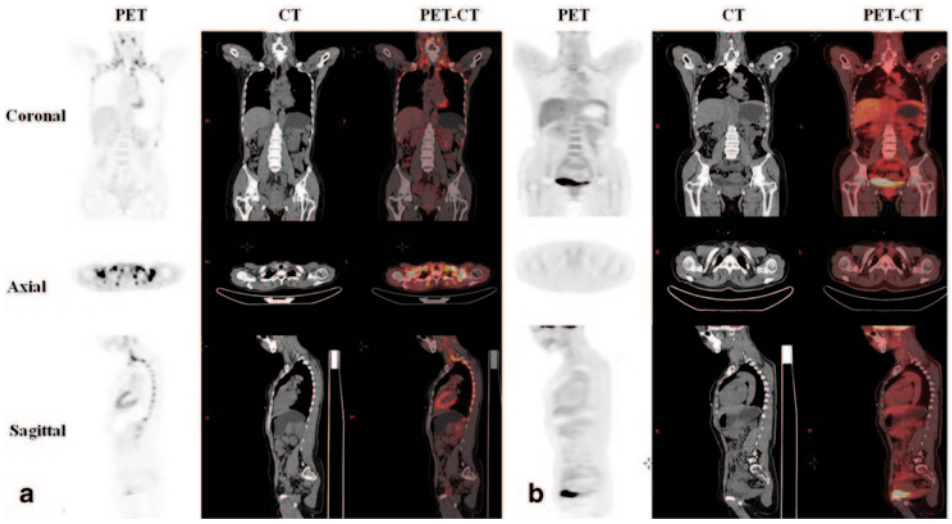

Fig. 2 The images of subjects with and without active brown adipose tissue assessed by PET-CT with [18F]FDG. **a** The image shows extended BAT uptake of [^{18}F]FDG in neck, supraclavicular, axillary, mediastinal, and paravertebral regions in healthy adult. **b** The image of the other subject in whom PET-CT was performed in the same day shows no BAT uptake of [^{18}F]FDG in the same regions

Measurements of blood samples

In this article, the blood samples of subjects were drawn in the fasting state (at least after an 8-h fast), just before the PET-CT scan. Plasma glucose and lipid levels were measured using an automatic biochemical analyzer (Hitachi 7600, Japan). Plasma insulin concentration was measured by radioimmunoassay (SIEMENS, ADVIA Centaur XP). Plasma estradiol and testosterone levels were measured by electrochemiluminescence immunoassay (Roche, MODULAR E170). Enzyme-linked immunosorbent assay kits were used to measure concentrations of leptin, adiponectin (Mercodia, Sweden), free fatty acid-binding protein-4 (FABP4; Biovendor, Czech Republic), and tumor necrosis factor-α (TNF-α; Anogen, Canada), according to the manufacturers' instructions.

Statistical analysis

All analyses were performed using the software SPSS (version 13.0). Stratified by gender, continuous variables were presented as means and standard deviations if normally distributed or as medians and interquartile ranges if asymmetrically distributed. Differences in the characteristics between the BAT-positive and BAT-negative groups were assessed using the Student's t test for normally distributed quantitative variables or the Mann–Whitney U test for asymmetrically distributed quantitative variables. The functions of age, BMI, smoking history, drinking history, and exercise as predictors of active BAT were tested by logistic regression using univariate and multivariate models. Odds ratios and 95% confidence intervals were estimated as measures of the magnitude of the associations. Multiple linear regression analysis was performed to examine the associations between active BAT and various metabolic indexes. All p-values presented are two-tailed, and values <0.05 are considered to be statistically significant.

Results

Clinical characteristics

The prevalence of active BAT in this group was 3.15% (79/2506). A total of 17 BAT-positive individuals were excluded due to failure to obtain a written consent or to find a negative control. Consequently, 62 pairs of subjects were recruited for this study (22 pairs male, 40 pairs female). In both male and female groups, BAT-positive individuals were younger than their controls (35.5±7.8 years vs. 39.9±6.4 years, $p=0.049$, in the male group; 38.0±6.7 years vs. 43.5±7.3 years, $p=0.001$, in the female group), and the BAT-positive group had a lower BMI (21.3±2.5 kg/m^2 vs. 24.2±4.3 kg/m^2, $p=0.004$, in the male group; 21.3±2.2 kg/m^2 vs. 22.5±2.5 kg/m^2, $p=0.026$, in the female group; Table 1). Compared with their negative controls, the BAT-positive males had a lower waist–hip ratio (WHR; 0.9±0.1 vs. 0.9±0.1, $p=0.020$). SBP/DBP and heart rate were not significantly different between the BAT-positive and BAT-negative groups.

Body composition

None of the recruited subjects were obese [BMI >30 kg/m^2 according to the 2005 World Health Organization criteria]. In the male group, BAT-positive subjects had a significantly lower fat percentage than the negative controls (19.5±5.9% vs. 24.7±4.4%, $p<0.001$; Table 1). However, this was not seen in the female group.

Lipid profiles

In both male and female groups, in contrast to negative controls, the level of high-density lipoprotein cholesterol (HDL-c) was significantly higher in BAT-positive subjects (1.6±0.3 mmol/l vs. 1.1±0.2 mmol/l and 2.0±0.5 mmol/l vs. 1.5±0.3 mmol/l, $p<0.001$, in both male and female

Table 1 Characteristics of the subjects and body composition[a]

Variable	BAT positive	BAT negative	*p*-value
Male (N = 22)			
Clinical characteristics			
Age (years)	35.5±7.8	39.9±6.4	0.049
SBP (mmHg)	127.0±14.2	124.6±9.7	0.883
DBP (mmHg)	77.1±19.4	80.4±8.1	0.340
Heart rate (beats/min)	74.1±10.2	68.4±8.0	0.106
Body composition			
BMI (kg/m^2)	21.3±2.5	24.2±4.3	0.004
Waist circumference (cm)	78.2±7.3	89.1±9.7	<0.001
WHR	0.9±0.1	0.9±0.1	0.020
Body fat (%)	19.5±5.9	24.7±4.4	<0.001
Female (N = 40)			
Clinical characteristics			
Age (years)	38.0±6.7	43.5±7.3	0.001
SBP (mmHg)	122.0±14.1	118.8±12.8	0.291
DBP (mmHg)	78.7±9.2	75.7±7.9	0.125
Heart rate (beats/min)	74.2±10.2	72.4±6.2	0.345
Body composition			
BMI (kg/m^2)	21.3±2.2	22.5±2.5	0.026
Waist circumference (cm)	76.3±6.2	78.9±6.2	0.069
WHR	0.8±0.1	0.8±0.1	0.819
Body fat (%)	29.3±4.0	30.5±3.3	0.152

SBP systolic blood pressure, *DBP* diastolic blood pressure
[a]Values are presented as means ± standard deviations; BMI (body mass index) is the weight in kilograms divided by the square of the height in meters; and WHR (waist-to-hip ratio) is the waist circumference in centimeters divided by the hip circumference in centimeters

Table 2 Metabolic variables of the subjects[a]

Variable	BAT positive	BAT negative	*p*-value
Male (N = 22)			
Lipid levels (mmol/l)			
Total cholesterol	4.9±1.2	4.9±1.0	0.781
LDL cholesterol	2.9±1.0	3.0±0.9	0.512
HDL cholesterol	1.6±0.3	1.1±0.2	<0.001
Triglycerides	1.1 (0.9–1.3)	1.3 (1.0–2.6)	0.093
TC/HDL[b]	3.1±0.7	4.5±1.2	<0.001
Glucose metabolism			
FPG (mmol/l)	4.7±0.4	5.0±0.6	0.029
Fasting insulin (pmol/L)[c]	20.2 (13.3–42.2)	39.7 (20.3–77.5)	0.026
HOMA-IR[d]	0.7 (0.5–1.5)	1.64 (0.7–2.9)	0.016
Female (N = 40)			
Lipid levels (mmol/l)			
Total cholesterol	5.1±0.8	4.9±1.1	0.501
LDL cholesterol	2.8±0.7	2.9±0.8	0.461
HDL cholesterol	2.0±0.5	1.5±0.3	<0.001
Triglycerides	0.9 (0.7–1.1)	0.8 (0.7–1.3)	0.081
TC/HDL[b]	2.7±0.5	3.4±0.8	<0.001
Glucose metabolism			
FPG (mmol/l)	4.8±0.4	4.8±0.4	0.772
Fasting insulin (pmol/L)[c]	20.1 (11.4–37.1)	29.9 (23.6–41.1)	0.006
HOMA-IR[d]	0.7 (0.4–1.2)	1.1 (0.8–1.4)	0.005

LDL low-density lipoprotein, *FPG* fasting plasma glucose
[a]Values are presented as means ± standard deviations if normally distributed or as medians (interquartile ranges) if asymmetrically distributed
[b]TC/HDL is the total cholesterol divided by the high-density lipoprotein
[c]Values for insulin were converted to picomole per liter by multiplying by 6.0
[d]HOMA-IR (homeostasis model of assessment—insulin resistance) was calculated using the following formula: the fasting glucose in millimoles per liter multiplied by fasting insulin in microunit per milliliter and divided by 22.5

groups, respectively; Table 2). The levels of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-c), and triglycerides (TGs) were not significantly different between BAT-positive and BAT-negative subjects. However, the TC-to-HDL ratio (TC/HDL) was significantly lower in BAT-positive populations than in negative controls (3.1±0.7 vs. 4.5±1.2 and 2.7±0.5 vs. 3.4±0.8, $p<0.001$, in both male and female groups, respectively; Table 2).

Fasting glucose and insulin

Compared with their negative controls, the BAT-positive males had significantly lower fasting glucose (4.7±0.4 mmol/l vs. 5.0±0.6 mmol/l, $p=0.029$) and fasting insulin levels [20.2 (13.3–42.2) pmol/l vs. 39.7 (20.3–77.5) pmol/l, $p=0.026$]. However, in the female groups, only the fasting insulin level of the BAT-positive subjects was significantly lower than that of negative controls [20.1 (11.4–37.1) pmol/l vs. 29.9 (23.6–41.1) pmol/l, $p=0.006$], whereas the fasting plasma glucose levels showed no difference (Table 2). The homeostatic model of assessment—insulin resistance (HOMA-IR) in the BAT-positive groups was significantly lower than that of the negative controls (0.7 vs. 1.6, $p=0.016$, in the male group; 0.7 vs. 1.1, $p=0.005$, in the female group; Table 2).

Adipokines and other biochemical markers

Leptin levels were significantly lower in both male and female BAT-positive individuals than in their negative controls [1.4 (1.0–1.8) ng/ml vs. 4.8 (2.6–8.8) ng/ml, $p<0.001$, in the male group; 7.9±4.8 ng/ml vs. 11.4±6.6 ng/ml, $p=0.008$, in the female group; Table 3]. However, adiponectin and FABP4 levels showed no significant difference.

In the male group, the level of TNF-α was significantly lower in BAT-positive individuals than in the negative controls [11.7 (10.9–12.4) pg/ml vs. 16.0 (14.1–17.8) pg/ml, $p<0.001$]. However, in the female group, there was no such difference between the BAT-positive individuals and their negative controls.

Due to differences in the prevalence of BAT between females and males [2], we investigated the levels of serum

Table 3 Adipokines and other biochemical markers of the subjects[a]

Variable	BAT positive	BAT negative	*p*-value
Male (*N* = *22*)			
Leptin (ng/ml)	1.4 (1.0–1.8)	4.8 (2.6–8.8)	< 0.001
Adiponectin (μg/ml)	8.1 ± 3.6	7.0 ± 2.6	0.252
FABP4 (ng/ml)	9.8 ± 5.5	10.4 ± 4.2	0.717
TNF-α (pg/ml)	11.7 (10.9–12.4)	16.0 (14.1–17.8)	< 0.001
Testosterone (nmol/L)	15.3 ± 6.3	17.9 ± 8.7	0.265
Female (*N* = *40*)			
Leptin (ng/ml)	7.9 ± 4.8	11.4 ± 6.6	0.008
Adiponectin (μg/ml)	8.9 ± 3.9	9.2 ± 2.9	0.690
FABP4 (ng/ml)	11.4 ± 4.5	12.7 ± 5.8	0.247
TNF-α (pg/ml)	13.4 (12.1–18.5)	14.9 (12.1–17.1)	0.603
Estradiol (pmol/L)	213.2 (145.3–455.1)	247.4 (75.3–593.7)	0.931

BAT brown adipose tissue, *TNF*-α tumor necrosis factor-α, *FABP4* free fatty acid-binding protein-4

[a]Values are presented as means ± standard deviations if normally distributed or as medians (interquartile ranges) if asymmetrically distributed

testosterone and estradiol to observe the relationship between BAT and these sex hormones. We found that, in male group, the testosterone levels were not significantly different between the BAT-positive subjects and the negative controls. Similarly, in female group, the estradiol levels were also not significantly different (Table 3).

Multiple linear regression models were performed to investigate the possible associations of active BAT with various metabolic indexes, and to elucidate the differences between the male and female groups. After adjusting for age, BMI, and body fat percentage, the levels of HDL, TC/HDL, and leptin remained significantly different between the BAT-positive and BAT-negative groups ($p < 0.0001$, $p < 0.005$, $p < 0.05$, respectively; Table 4).

Predictors of active brown adipose tissue

Because the gender and date of PET-CT scan in two groups were matched, the gender and outdoor temperature were not considered as predictors. In univariate analyses, BAT was more frequently detected in young subjects ($p = 0.001$), slender individuals ($p = 0.002$), and those who had exercised more often ($p = 0.005$; Table 5). In multivariate analyses, two predictors (age and exercise) remained significant. Thus, BAT was found most frequently in young subjects ($p = 0.002$) and in individuals who participated more in exercise and sports ($p = 0.002$; Table 5).

Discussion

PET-CT has long been used to detect malignant tissue. Moreover, it is often used for medical check-ups in some clinic centers worldwide. In China, some individuals undergo PET-CT scan only for health assessment. This

Table 4 Multiple linear regression models were performed for associations of active BAT with various metabolic indexes[a]

Variable	Model	Male			Female		
		β	SE	P	β	SE	P
Lg (HOMA-IR)[b]	1	−0.5	0.2	0.05	−0.4	0.2	0.05
	2	−0.39	0.2	0.22	−0.3	0.2	0.07
	3	−0.3	0.3	0.32	−0.3	0.2	0.07
FBG	1	−0.2	0.2	0.18	−0.01	0.1	0.90
	2	−0.1	0.2	0.42	−0.001	0.1	0.99
	3	−0.2	0.2	0.34	−0.01	0.1	0.91
Lg (insulin)[b]	1	−0.4	0.2	0.07	−0.4	0.2	0.05
	2	−0.3	0.2	0.25	−0.3	0.2	0.07
	3	−0.2	0.2	0.37	−0.3	0.2	0.08
TC	1	0.01	0.4	0.98	0.4	0.2	0.12
	2	0.2	0.4	0.60	0.4	0.2	0.09
	3	0.2	0.4	0.55	0.4	0.2	0.09
Lg (TG)[b]	1	−0.3	0.2	0.11	0.03	0.1	0.74
	2	−0.1	0.2	0.48	0.05	0.01	0.62
	3	−0.1	0.2	0.62	0.04	0.1	0.68
HDL	1	0.4	0.1	<0.0001	0.5	0.1	<0.0001
	2	0.4	0.1	<0.0001	0.5	0.1	<0.0001
	3	0.4	0.1	<0.0001	0.5	0.1	<0.0001
LDL	1	−0.2	0.3	0.6	0.04	0.2	0.8
	2	−0.04	0.3	0.9	0.1	0.2	0.63
	3	0.003	0.3	0.99	0.1	0.2	0.71
TC/HDL	1	−1.3	0.3	0.0001	−0.7	0.2	0.0001
	2	−1.0	0.3	0.001	−0.6	0.2	0.0001
	3	−0.9	0.3	0.002	−0.6	0.2	0.0001
Lg (letpin)[b]	1	−1.2	0.2	<0.0001	−2.9	1.4	0.04
	2	−0.9	0.2	<0.0001	−2.3	1.1	0.04
	3	−0.8	0.2	<0.0001	−2.7	1.1	0.01
Adiponectin	1	1.0	1.0	0.34	−0.2	0.8	0.83
	2	0.6	1.0	0.59	−0.4	0.8	0.66
	3	0.1	1.0	0.93	−0.4	0.8	0.66
FABP4	1	−0.7	1.6	0.64	0.03	1.2	0.98
	2	1.0	1.4	0.47	0.5	1.0	0.67
	3	1.9	1.3	0.17	0.3	1.0	0.75
Lg (TNF-α)[b]	1	−0.2	0.3	0.48	0.06	0.2	0.73
	2	−0.2	0.3	0.53	0.03	0.2	0.87
	3	−0.3	0.3	0.43	−0.01	0.2	0.94
WHR	1	−0.03	0.02	0.06	0.04	0.01	0.76
	2	−0.01	0.01	0.47	0.01	0.01	0.52
	3	−0.01	0.02	0.63	0.01	0.01	0.49
Fat %	1	−4.0	1.5	0.01	0.3	0.8	0.75
	2	−1.8	1.2	0.14	0.6	0.6	0.26

HOMA-IR homeostasis model of assessment—insulin resistance, *FBG* fasting blood glucose, *TC* total cholesterol, *TG* trigliceride, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *FABP4* free fatty acid-binding protein-4, *TNF*-α tumor necrosis factor-α, *WHR* waist–hip ratio

[a]Values of β are regression coefficients: model 1, after adjustment for age; model 2, after adjustment for age and body mass index; model 3, after further adjustment for fat percentage

[b]Logarithmic transformation was used to transform data to normal distribution, and described as Lg (X) instead of X

Table 5 Predictors of active brown adipose tissue based on positron emission tomography–computed tomography scanning[a]

Variable	Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	*p*-value	Odds ratio (95% CI)	*p*-value
Age (+10 years)	0.4 (0.2–0.6)	0.001	0.3 (0.2–0.7)	0.002
BMI (+1 kg/m^2)	0.8 (0.7–0.9)	0.002	0.9 (0.7–1.0)	0.077
Smoking history (Yes vs. No)	0.9 (0.4–2.2)	0.823	0.8 (0.2–3.1)	0.750
Drinking history (Yes vs. No)	1.1 (0.5–2.2)	0.855	0.9 (0.4–2.4)	0.850
Exercise (Yes vs. No)	3.2 (1.4–7.2)	0.005	4.7 (1.8–12.2)	0.002

CI confidence interval
[a]Age and body mass index (BMI) are continuous variables, and smoking history, drinking history, and exercise are categorical variables

was true for our cross-sectional study examining healthy adults in an un-stimulated state. The current study also used a larger sample than previous studies [3, 4].

Our findings supports previous findings that adults with active BAT are younger and have a lower BMI than those without active BAT [3, 11, 12]. Compared with their BAT-negative controls, the BAT-positive males had a lower WHR and percentage of fat mass, whereas no such difference was found in females. Our results suggest that active BAT may be related to body weight regulation and fat distribution in the un-stimulated state. Our results show, for the first time, that adults, both males and females, with active BAT in the un-stimulated state have a higher level of HDL and a lower level of insulin and HOMA-IR than those without active BAT, although TG level is not significantly different.

Metabolic disorders are often accompanied by dyslipidemia, insulin resistance, hyperglycemia, systemic inflammation, and adipokine dysregulation [13, 14], and the adipokines secreted from the adipose tissue are able to affect whole-body energy homeostasis [15]. Thus the serum TNF-α, leptin, and adiponectin levels were also investigated in the current study. The BAT-positive group had a significantly lower level of leptin than the BAT-negative group in both males and females, and the BAT-positive males had a significantly lower level of TNF-α than the negative control males; however, no significant difference was found between BAT-positive and BAT-negative females. The reduced TNF-α and fasting glucose levels might be secondary to lower BMI and body fat content in male BAT-positive group.

It is well known that TNF-α is positively associated with insulin resistance and insulin sensitivity, and adipokines are closely associated with BMI and body fat content [16–18]. The beneficial metabolic profiles in the BAT-positive group may be partly due to a lower BMI and body fat percentage. Multiple linear regression analyses were performed to investigate the possible associations of active BAT with various metabolic indexes, and to elucidate the differences between the male and female groups. After adjusting for age, BMI, and the body fat percentage, only HDL levels, TC/HDL, and leptin levels remained significantly different between the BAT-positive and BAT-negative groups.

Recently Bartelt et al. [19] demonstrated that cold-induced activation of BAT in mice leads to a significant reduction in circulating TG levels as a result of increased uptake of TG by BAT and a slight elevation of HDL levels likely due to an increase in TG-rich lipoprotein-derived HDL precursors. In humans, Van Marken Lichtenbelt et al. [2] examined the presence and activity of BAT in healthy volunteers and its relation to body composition and energy expenditure under both thermoneutral (22 °C) and mild cold exposure (16 °C) conditions; however, changes in lipid profiles along with the cold-induced activation of BAT were not investigated. Our study found a significant and independent difference in HDL levels and TC/HDL along with active BAT after adjusting for BMI and fat percentage. HDL is a well-known protective factor for cardiovascular disease, and a European prospective study showed that elevated TC/HDL ratios are directly related to the incidence of coronary heart disease, and are independent of any other single lipid abnormality [20]. Our results found that adults with active BAT in an un-stimulated state had higher levels of HDL, although the possible mechanisms and the potential clinical significance need further investigation.

Leptin is one of the most important circulating adipokines. Mainly secreted from white adipose tissue, it regulates body weight by decreasing appetite and increasing sympathetic nerve activity in mice, which increases energy expenditure in BAT [21, 22]. Studies in animals and humans show that the circulating leptin level is proportional to BMI and fat mass [22]. Most of these studies focused on the effects of central or intravenous leptin administration on the activity of BAT and the expression of leptin in BAT [23, 24]. Results in rodents show that leptin can increase the activity of BAT [25]. In 2001, Margareto et al. [22] found a significant positive association between the interscapular BAT uncoupling protein 1 (UCP1) and serum leptin levels. However, in 2006, Wang et al. [26] found that serum leptin levels were positively correlated with body mass and body fat mass, but negatively correlated with the UCP1 protein content of BAT in voles. Our study reported, for the first time, the difference in serum leptin levels between adults with and without active BAT in an un-stimulated state. Serum leptin level was lower in the BAT-positive group than in the BAT-negative group, whereas the BAT-positive group had a lower BMI and fat percentage than the negative control group. After adjusting for the BMI and fat percentage, serum leptin levels remained different in the BAT-positive vs.

BAT-negative group, suggesting that BAT activity may directly affect circulating leptin levels. In 1998, Cancello et al. [27] found that in brown adipocytes of warm-acclimated mice, leptin mRNA and protein expression was higher at 28 °C than at 19 °C, whereas the change of UCP1 expression was opposite. In 2008, Korac et al. [28] found that the leptin expression in BAT was suppressed in cold-acclimated rats compared with room temperature-acclimated rats. These findings in animals are consistent with those found in humans. Therefore, the lower level of serum leptin in adults with active BAT may be attributed to the lower BMI and fat mass as well as its decreased expression in active BAT.

In 2009, Cypess et al. [3] performed a retrospective study indicating that the probability of the detection of BAT was inversely correlated with BMI, age, outdoor temperature, and beta-blocker usage. In the current study, the relationship between BAT and living habits was also addressed. Univariate analysis showed an inverse correlation between the prevalence of detectable BAT and age and a direct correlation between BAT and exercise; after multivariate analysis, this correlation persisted. These results suggest that active BAT may protect against age-related metabolic disorders [29]. Furthermore, our study suggests that exercise may raise the activity of BAT. Previous studies done in animals showed that exercise training potentiated BAT thermogenesis, which reduced the body weight in OVX obese rats [30]. Recently, a new hormone, irisin, was discovered in another study in animals. In that study, this hormone improved with exercise and stimulated UCP1 expression as well as a broad program of brown-fat-like development [31]. Thus, approaches for increasing BAT mass and/or stimulating its activity, such as increased physical activity, may promote metabolism. There are certain limitations in the current study. Due to methodological constraints, quantification of BAT activity and further analysis of the correlations between BAT activity and other factors were not performed. Insulin sensitivity was evaluated by HOMA-IR instead of the gold standard clamp.

In summary, our results indicate that healthy adults with active BAT in an un-stimulated state have a favorable metabolic status, especially with a higher level of HDL and a lower level of leptin, which is independent of other factors. Active BAT might be a candidate for improving metabolic conditions in humans, thus providing a new therapeutic target for combating obesity, diabetes, hyperlipidemia, and other metabolic disorders.

Grant support

This study was supported by grants (No.10JC1401002, No.11PJ1402000) from the Shanghai Committee of Science and Technology, China, (No.30771024, No.30900502 and No.81070680) from the National Natural Science Foundation of China, (No.XYQ2011002) from the Shanghai Municipal Health Bureau, (No.09FQ71) from the Young Science Fund of Fudan University, (No.2009056) from the Institutes of Biomedical Sciences of Fudan University, (No.EYF151063) from the Graduate Innovation Fund of Fudan University, (No.2011CB910201) from the National Basic Research Program of China (973 Program), and (No.985III-YFX0302) from the 985 Project.

Acknowledgments

The authors thank the staff of PET Center (Huashan Hospital) for their help in performing the study, the staff from Division of Endocrinology and Metabolism and the Center of Laboratory Medicine (Huashan Hospital) for their technical assistance, and the subjects for their participation in the study.

Conflict of interest

No potential conflicts of interest relevant to this article were reported.

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