The Prevalence and Characteristics of Brown Adipose Tissue in an ^{18}F -FDG PET Study of Koreans

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Abstract

Purpose The object of this study was to evaluate the prevalence and characteristics of brown adipose tissue (BAT) in Korean subjects using ^{18}F -fluorodeoxyglucose positron emission tomography (^{18}F -FDG PET).

Methods Six thousand and five consecutive ^{18}F -FDG PET/CT scans of 5,115 patients (3,007 females and 2,108 males, mean age 53.5 years) were retrospectively reviewed. We characterized the nature of BAT, such as its location, and we assessed the influence of sex, age, body mass index (BMI), and temperature on BAT.

Results The prevalence of BAT in Koreans in a single ^{18}F -FDG PET/CT scan in average conditions was 1.07%. The BAT detection rate was higher in females than males (1.32% vs 0.73%), and also with younger age (7.94% vs 0.73%), lower BMI (BMI with BAT, 21.1 vs BMI without BAT, 23.15) and cold outdoor temperature (1.65% vs 0.49%). The most frequent location of BAT was the supraclavicular area (left, 0.91%; right, 0.88%) and ventral neck area (left, 0.62%; right, 0.63%).

Conclusions The characteristics of BAT in Koreans are not different from those described for Caucasians. However, the

low prevalence of BAT in our study might be related to some scan condition like ambient temperature, but further study is needed.

Keywords Brown adipose tissue · FDG · PET · Korean

Introduction

Positron emission tomography (PET) using ^{18}F -fluorodeoxyglucose (^{18}F -FDG) plays an important role in the evaluation of cancer [1]. Although PET is highly sensitive for the detection of malignancy, ^{18}F -FDG uptake in other benign tissues, including BAT, has been well documented [2]. The recent introduction of hybrid PET/computed tomography (CT) scanners has allowed the accurate co-registration of morphological and metabolic information, which has enabled precise localization of ^{18}F -FDG uptake within distinct anatomical structures [3–5]. As a result, most previously reported physiological uptake of ^{18}F -FDG PET has been brown adipose tissue (BAT) [6, 7].

The physiologic characteristics of BAT are not well established. BAT has been hypothesized to be the cause of increased metabolic activity in fat tissue [6, 7]. BAT is known to be linked to the resting metabolic rate and thermogenesis, with high individual variation [8]. Individual differences in BAT or energy expenditure can have large, long-term effects on body weight [9]. Several prospective studies have shown that a relatively low energy expenditure predicts a gain in body weight [10, 11]. Obesity is linked with low incidence of BAT [12]. The prevalence of BAT is not known in Koreans, but is 2.3–4% in other countries [6, 13].

The purpose of this study was to determine the prevalence and characteristics of BAT in Korean subjects

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by PET exam. Further, we sought to evaluate whether BAT is influenced by age, sex, and temperature. This information might be useful in identifying BAT from cancerous lesions and in studying metabolic disease like obesity.

Materials and methods

Six thousand and five consecutive whole-body scans of 5,115 subjects (3,007 females and 2,108 males) were reviewed for the presence of BAT. The scans were obtained using an ^{18}F -FDG PET/CT scanner from January to December 2007. All scans were taken for the evaluation of known or suspected malignancy. Scanning was performed using the Discovery LS PET/CT scanner (General Electric Medical Systems, Milwaukee, Wis., USA) and Biograph 6 PET/CT scanner (Siemens Medical Solutions, Malvern, Pa., USA). Each scan was obtained following the protocol. Subjects were fasted at least 6h before the PET acquisition. Intravenous injection of 440 ± 60 MBq ($165\text{--}758$ MBq) of ^{18}F -FDG was followed by a tracer uptake phase of about 60 min, during which the subjects sat in a quiet, dimly lit room without talking.

CT Scanning

The CT portion of the Discovery LS consists of a multidetector helical scanner (LightSpeed Plus; General Electric Medical Systems) and Biograph 6 utilizes a six-slice CT. Imaging parameters were as follows for an acquisition at five to seven bed positions: 140 kV, 80 mA, 0.8 s per CT rotation, a pitch of 6, a table speed of 22.5 mm/s, 722.5- to 1,011.5-mm coverage, a 31.9- to 37-s acquisition time for Discovery LS and 130 kV, 30 mA, 0.6 s per CT rotation, a pitch of 1.5, 20.89-s acquisition time for Biograph 6. The CT scan was performed before emission PET scans. The current of the CT tube was adjusted according to patient weight. The CT data were resized from a 512×512 matrix to a 128×128 matrix to match the PET data in order to generate a CT transmission map and to fuse images.

PET Scanning

PET emission data were acquired for five to seven bed positions, typically from the base of the skull through the upper thigh. Emission data were acquired for 6 min for each bed position. Each bed had 35 (for Discovery LS) or 39 (for Biograph 6) scanning planes with a 14.6-cm (for Discovery LS) or 16.2-cm (for Biograph 6) longitudinal field of view and a one-slice overlap. PET images were reconstructed using CT for attenuation correction with the ordered-subsets expectation maximization algorithm (two iterations,

eight subsets) and a 5-mm Gaussian filter using a 128×128 matrix.

Image Analysis

All PET/CT scans were examined retrospectively by one observer on an interactive computer display using fusion software (Xeleris; General Electric Medical Systems and Syngo; Siemens Medical Solutions). This software allowed the review of PET, CT, and fused data using transaxial, sagittal, and coronal displays. BAT was considered present if there was ^{18}F -FDG uptake with specific patterns (clusters of round foci of increased activity in a curvilinear pattern), which are different from lymph node and muscle uptake as described in the literature based on PET/CT [13], and after exclusion of malignancy and other structures.

PET images were evaluated for the presence of obvious abnormally increased ^{18}F -FDG standardized uptake value (SUV) (i.e., more intense than background activity, Fig. 1) with corresponding fat-density tissue (-250 to -50 Hounsfield units) in the fused and CT images [7]. The monthly outdoor temperature (minimum, maximum, and average) of Seoul city, where the PET/CT scanners were installed, was obtained from the web site of the Korean Meteorological Administration (<http://www.kma.go.kr>). Patients with at least one study demonstrating BAT and with serial scans available were analyzed subsequently.

Statistical Analysis

Results were expressed as mean $\pm$ SD. Differences in the incidence of BAT were tested by χ^2 test. Differences in age and body mass index (BMI) between the groups with and without BAT were tested by independent *t*-test. Two-tailed *p* values less than 0.05 were considered significant.

Results

Characteristics of the Subjects

The patient population comprised of total 5,115 (2,108 males/3,007 females) and the age range was 3–83 years (53.5 ± 15.5 years). The average SUV of BAT was 2.90 ± 1.80 .

The Prevalence and Sex Difference of BAT

Sixty-four scans (1.07%) from the 6,005 scans were judged to be positive for BAT. Sixty-three subjects (1.02%) from the 5,115 patients were positive for BAT. Females showed more positive BAT than males [45 of 3,408 (1.32%) vs 19

Fig. 1 BAT activity, as assessed by ^{18}F -FDG PET/CT, in a 15-year-old boy. Increased ^{18}F -FDG uptake is shown in the BAT of the bilateral ventral neck (VN), mediastinum (ME), supraclavicular (SC) and paravertebral (PV) areas

of 2,597 (0.73%), $p = 0.04$]. Subjects with BAT were younger than subjects without BAT (30.67 ± 15.37 years vs 53.79 ± 15.13 years, $p < 0.001$). Males were younger than females among subjects with BAT (19.68 ± 11.98 years vs 35.31 ± 14.33 years, $p < 0.001$).

The Influence of Age on BAT

The prevalence of BAT decreases with age (Table 1). Twenty-two of 277 patients (7.9%) under the age of 18 years showed ^{18}F -FDG uptake by BAT, compared with 41 of 5,729 patients (0.73%) who were 18 years or older ($p < 0.0001$).

In young subjects less than 18 years old, the prevalence of BAT between boys and girls was not different although male predominance (8.3% vs 7.4%, $p = 0.3474$). In older subjects

more than 18 years of age, the prevalence of BAT in males was lower than females (2.2% vs 0.4%, $p < 0.0001$).

The Influence of BMI on BAT

There was a significant difference in BMI between subjects with BAT and without BAT (Table 2). However, there was no significant difference in BMI between male and female groups with or without BAT.

The Influence of Temperature on BAT

Figure 2 demonstrates the monthly incidence of BAT and its temporal relationship to the average monthly temperature. The highest prevalence of ^{18}F -FDG uptake by BAT occurred in November (6.3%) and December (6.2%). July had the lowest prevalence (0%). The incidence of BAT was higher from November to April compared with from May to October, corresponding to the lower monthly temper-

Table 1 The prevalence of BAT by age and sex groups

Sex	Age group (years)				
	Under 18	18–29	30–39	49–50	Above 50
Male	13/156 (8.3%)	2/97 (2.1%)	2/161 (1.2%)	2/360 (0.6%)	0/2,095 (0%)
Female	9/121 (7.4%)	6/87 (6.9%)	16/324 (4.9%)	5/781 (0.6%)	9/1,823 (0.5%)
Total	22/277 (7.9%)	8/184 (4.3%)	18/485 (3.7%)	7/1,141 (0.6%)	9/3,918 (0.2%)

Table 2 BMI of both sex groups with and without BAT

Sex	With BAT	Without BAT	p value ^a
Male	20.35 ± 3.40	22.87 ± 3.25	0.0008
Female	21.41 ± 3.40	23.36 ± 3.52	0.0002
Total	21.10 ± 3.41	23.15 ± 3.42	<0.0001

^a Independent t -test

Fig. 2 Monthly incidence of BAT and its relationship to the average monthly temperature

atures (lowest monthly temperature $<10^{\circ}\text{C}$ vs $>10^{\circ}\text{C}$) (1.65% vs 0.49%, $p < 0.01$). In young subjects (<18 years), there was no difference between November to April and May to October (9.6% vs 6.6%, $p = 0.48$).

Anatomical Distribution of BAT

In the 64 scans (63 subjects) with BAT, supraclavicular uptake was most common. Supraclavicular uptake was seen in 55 scans following the ventral neck, paravertebral, axillary and mediastinal area (Table 3).

Of the 55 studies showing supraclavicular uptake, paravertebral uptake was also seen in 27 (68%), axillary uptake in 23 (58%), mediastinal uptake in 23 (58%), and ventral neck in 11 (28%). Alternatively, of the 29 studies showing paravertebral uptake, all but two studies (93%) also had concomitant supraclavicular uptake. No studies showed isolated mediastinal uptake.

Repeated Scans

Among the 63 patients with BAT, 24 underwent 74 scans during the survey period. Only one subject show BAT twice over three scans.

Discussion

In this study, the prevalence of BAT in Korean subjects in a single scan in average conditions was 1.07%, while the characteristics of BAT were the same as in previous

studies. The BAT detection rate was high with cold outdoor temperature, younger age, lower BMI, and female sex. The most frequent location of BAT in Koreans is supraclavicular and the ventral neck area. This prevalence is relatively low compared with those reported in the previous literature, which ranges from 2.3 to 4% [6, 7, 13–16]. The lower BAT detection rate in our study is not known. One possible explanation might be differences in scan conditions like temperature and fasting. It is well known that feeding and cold stress influence BAT activity in mice and humans [17, 18]. BAT activity was different according to ambient temperature. Our study, like others, showed a high prevalence during winter time compared with summer time. In children, the prevalence of BAT uptake increased from 5% to 31% by change in temperature from 24°C to 21°C [18]. Our study subjects were all known or suspected cancer patients. However, the routine examination procedures of cancer patients include a 4- to 24-h fasting period (to decrease blood glucose that dilutes FDG), and fasting leads to a diminished activity of BAT [19]. However, the other previous studies reporting BAT prevalence also included most cancer patients [6, 13]. The other possible explanation might be some ethnic difference in BAT pattern. However, a comparative study of race and ethnicity for BAT has not been done previously. Whether there is some ethnically related metabolic difference needs further study. The “true” prevalence of BAT is impossible to know in a clinical setting. The importance of this study was that in clinical conditions the prevalence of BAT in Koreans was 1.07%. As shown in our subjects with BAT, the detection rate of 45%, as described previously, was not reproducible [20].

The prevalence of BAT decreased over age. In mice, the prevalence of BAT increased until 6 months of age, and then decreased thereafter. Similarly, we found in humans that the prevalence increased until young adulthood and decreased thereafter. One interesting finding in this study is that BAT occurrences abruptly decrease after age 40 years. The prevalence of BAT over age 40 is 0.31% (16 of 5,061). It was consistent with the study including patients in their 50s, 60s, or even 70s [14].

The prevalence of BAT in females was high when compared with men, as shown in the previous studies [6, 7]. The increased mass of BAT in female rats, when compared

Table 3 Incidence of BAT uptake in five areas ^a

	Supraclavicular	Ventral neck	Paravertebral	Axilla	Mediastinum
Left	55 (0.91%)	37 (0.62%)	23 (0.38%)	12 (0.20%)	4 (0.06%)
Right	53 (0.88%)	38 (0.63%)	24 (0.40%)	12 (0.20%)	4 (0.06%)

^a Frequency (%) per total 6,005 studies

with male rats, was known [21]. In humans, females exhibit more BAT than males [7]. BAT is rich in sympathetic nerves and known to generate heat under cold stimulation. Females experience more acute cold stress during the time of ^{18}F -FDG uptake. So the threshold of BAT activity of females is lower than males in clinical conditions. However, there was no difference between the sexes in subjects younger than 18 years old, which means the influence of aging is more powerful than that of sex on BAT activity.

One of the important issues is whether the presence of active BAT in humans would be protective against obesity. This study showed that the BAT activity was higher in subjects with a low BMI, as in a previous study [20]. In rodents, some studies infer that BAT is anti-obesogenic by energy expenditure [22], but not all studies [23]. In humans, there is a correlation between the possession of active BAT and a low BMI [20], although others claim that such correlations do not exist [7, 14].

The most common location for BAT in our study was the supraclavicular area and ventral neck, paravertebral, axillary and mediastinal uptake, as previously described [24]. Most BAT showed symmetrical distribution, with little exception. When uptake in such sites is linear and bilateral, BAT may be suspected. Most paravertebral BAT coexisted with supraclavicular BAT. Of the supraclavicular BAT, 68% had paravertebral uptake. In addition, the intensity of the supraclavicular and paravertebral uptake was similar. These findings would be helpful in distinguishing BAT from malignancy.

We admit some limitations exist in our study. The actual temperature condition during individual scanning was not available because this was a retrospective study. The actual temperatures of imaging rooms might be influenced by air conditioning or heating. The prevalence of BAT could have been underestimated because milder cases or isolated BAT in atypical locations. Nevertheless, we believe that this factor was not a major concern in our study. Another limitation of this study is the lack of histopathologic confirmation of BAT. However, we used PET/CT in our evaluation and all malignancy was ruled out by following the scan and clinical data.

In conclusion, we have shown the prevalence and characteristics of BAT in Koreans. The prevalence is quite low compared with other studies, mostly in western countries. Whether it is an ethnic difference in metabolism or the scan conditions needs further study. This information might be useful when differentiating malignancy from benign conditions like BAT. It could also be very useful for metabolic diseases such as obesity and type 2 diabetes.

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