

A critical appraisal of the prevalence and metabolic significance of brown adipose tissue in adult humans

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¹Department of Endocrinology, St Vincent's Hospital; ²Garvan Institute of Medical Research; Department of PET and Nuclear Medicine, ³Royal Prince Alfred Hospital, Camperdown; ⁴Sydney Medical School, University of Sydney; and ⁵Faculty of Medicine, University of New South Wales, Sydney, New South Wales, Australia

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Lee P, Greenfield JR, Ho KK, Fulham MJ. A critical appraisal of prevalence and metabolic significance of brown adipose tissue in adult humans. *Am J Physiol Endocrinol Metab* 299: E601–E606, 2010. First published July 6, 2010; doi:10.1152/ajpendo.00298.2010.—Brown adipose tissue (BAT) plays a major role in energy homeostasis in animals. Detection of BAT using positron emission tomography (PET)-CT in humans has challenged the view that BAT disappears after infancy. Several recent studies, based on analysis of single scans, have reported a low prevalence of only 5–10% in humans, casting doubt on its significance. We undertook a critical analysis of the sensitivity, reproducibility, and accuracy of PET-CT to deduce the prevalence of BAT and factors associated with its detection in adult humans. In a retrospective evaluation of PET-CT, using [¹⁸F]fluorodeoxyglucose, performed in 2,934 patients, BAT was identified in 250 patients, yielding an apparent prevalence of 8.5%. Among those patients with BAT, 145 were scanned more than once. The frequency of another scan being positive increased from 8 to 65% for one to more than four additional studies. The average probability of obtaining another positive scan among patients with BAT is 13%, from which the prevalence of BAT is estimated at 64%. BAT was more commonly detected in women, in younger (36 ± 1 vs. 52 ± 1 years, $P < 0.001$) and leaner (20.1 ± 0.9 vs. 24.9 ± 0.9 kg/m², $P < 0.01$) individuals. Fasting glucose was lower in those with BAT than those without (4.9 ± 0.1 vs. 5.5 ± 0.1 mmol/l, $P < 0.01$). Among patients scanned more than once, BAT was detected when body weight and fasting glucose were lower (54.9 ± 0.5 vs. 58.2 ± 0.8 kg, $P < 0.001$ and 4.9 ± 0.3 vs. 5.5 ± 0.3 mmol/l, $P = 0.03$). We conclude that BAT is present in the majority of adult humans. Presence of BAT correlates negatively with body mass index and glucose concentration. BAT may play an important role in energy homeostasis in adults.

positron emission tomography; obesity; glucose

THE RISE IN TYPE 2 DIABETES is occurring worldwide in parallel with an increasing prevalence of obesity. Obesity is associated with significant morbidity and mortality. The latest National Health and Nutrition Examination survey revealed that one-third of adults were obese in 2007–2008 (8). Weight loss improves glycemic control and decreases mortality in people with type 2 diabetes (23, 24). Current approaches to combat obesity have limited efficacy, and new insights into adipose tissue biology may help devise novel approaches to reduce obesity.

There are two types of adipose tissue, white (WAT) and brown (BAT) (14). WAT functions mainly as a site of lipid storage and is used during times of caloric shortage. BAT is a key regulator in energy balance and metabolism in animals (4).

It plays a major role in thermogenesis and protects small mammals and human neonates from hypothermia. BAT expresses a unique protein, uncoupling protein-1 (UCP1), which uncouples oxidative phosphorylation and releases energy stored in the mitochondrial proton electrochemical gradient as heat. BAT activation of lipolysis and thermogenesis protects rodents against obesity and diabetes (1, 4, 11, 16).

In adult humans, BAT has been considered unimportant. It was thought to be present only in newborns and rapidly lost within the first few years of life (13). The emergence of PET using [¹⁸F]fluorodeoxyglucose, an analog of glucose ([¹⁸F]FDG-PET) has challenged this view (15). PET-CT has identified adipose tissue of high metabolic activity in the cervical-supraclavicular regions in adult humans (9). Histological examination of biopsies from this region revealed adipocytes with multilobulated lipid droplets, typical of brown adipocytes, which were strongly immunoreactive for UCP1 (19, 21, 22, 26).

The advent of functional metabolic imaging has fueled a resurgence of interest in BAT in humans. However, there is limited information on its physiology or metabolic significance in adult humans. Several recent studies have reported a low prevalence of only 5–10% in humans, casting doubt on its significance (2, 5–7, 12, 17, 25). However, the applicability or appropriateness of using standard PET-CT for BAT detection is not known but is an important issue because poor diagnostic sensitivity may underestimate its prevalence, obscuring physiological relationships. We have undertaken a critical analysis of the sensitivity and reproducibility and accuracy of PET-CT to deduce the prevalence of BAT. To investigate metabolic significance, we have determined whether BAT is related to body weight and glucose levels.

METHODS

Patients and PET-CT. The study population comprised 2,934 patients (36 ± 14 yr old; age range 18–87 yr; female 1,848) with a diagnosis of cancer (lymphoma 40%; lung malignancies, mainly non small cell lung cancer 20%; soft tissue sarcoma 15%; gastrointestinal tract, mainly colorectal carcinoma, 10%; head and neck 4%; breast 3%; and others 8%) who underwent FDG PET-CT for staging or restaging. This was a consecutive cohort of patients who were scanned at Royal Prince Alfred Hospital, Sydney between 2003 and 2008. These patients were identified by the typical pattern of FDG uptake in the soft tissues (fat) of the upper torso that was readily identified on PET-CT (Fig. 1). A retrospective analysis was undertaken on the 4,834 PET-CT scans performed on these patients for presence of BAT. Two PET-CT tomographs were used in the study: a Biograph Duo (Siemens, Hoffman Estates, IL) with LSO (lutetium orthosilicate) detectors and Biograph Truepoint, a 64-slice PET-CT scanner (Siemens). Patients were fasted for 6 h prior to the study. All patients

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Fig. 1. Transaxial fluorodeoxyglucose (FDG) PET (left), CT (middle), and fused PET-CT images (right) in an 18-yr-old woman. Increased FDG uptake is noted in the supraclavicular fossae on the PET image (black arrows); fused PET-CT image shows that increased FDG uptake is located in fat density in the soft tissues of both supraclavicular fossae.

were injected with 385 MBq of FDG. The uptake period was 60 min; the patients rested quietly in a room at a temperature of $\sim 21^{\circ}\text{C}$ prior to moving to the scanning room.

Data collection. The age, sex, height, weight, diagnosis, and fasting capillary glucose level of each patient prior to isotope injection were routinely recorded. Two experienced PET physicians read each PET-CT scan. BAT was considered present (a “positive” scan) if there were tissues with a maximal standard uptake value (SUV) of FDG of at least 2.0 within tissues delineated as fat on CT (-250 to -50 Hounsfield units). As a matter of routine, the presence of FDG uptake in BAT was reported in the scan report for the benefit of the referring clinicians, because, as shown in Fig. 1, the FDG uptake can be intense and of similar intensity to that seen with high-grade tumors. A keyword search of the phrase “brown fat” in the PET-CT report identified those with BAT. The PET-CT images and reports were stored in the Departmental Information System and were available for rapid access, via a web interface, and review. A third independent observer (PL) reviewed all reports that contained the phrase “brown fat” and examined each scan to verify the presence of BAT.

An open biopsy was obtained from adipose tissue with high FDG uptake in the neck region of one patient who underwent PET-CT study for staging prior to neck operation. A biopsy was obtained concurrently from subcutaneous neck fat as negative control. Fat biopsies were fixed in 10% formalin and moulded in paraffin. Tissue sections were stained with hematoxylin-eosin (HE) and rabbit polyclonal antibody to UCP1 (1:500, Abcam). Slides were imaged using an Eclipse E800 microscope (Leica, Heerbrugg, Switzerland).

To determine scan-rescan reproducibility, we evaluated the number of positive scans in 747 patients who were scanned more than once. Among these patients, 145 had at least one positive scan.

To determine metabolic parameters associated with BAT, 1) we compared the age, body mass index (BMI), and fasting glucose levels between patients with and without BAT; and 2) in the subgroup of patients ($n = 145$) who were scanned more than once, we compared body weight and fasting glucose levels on occasions when they were PET-CT positive with occasions when they were PET-CT negative.

BAT activity has been hypothesized to induce cancer cachexia, and increased BAT activity has been reported in children with malignant disease (3, 20). Therefore, the relationship between malignant disease activity and presence of BAT was analyzed in the latter subgroup. It is known that in rodents both acute and chronic environmental temperatures regulate BAT activity (1–4). Thus, we obtained the records of outdoor temperatures in Sydney from the Australian Weather Zone (www.weatherzone.com.au) for each study date to determine the influence of temperature in our analysis of the subgroup with more than one scan.

Statistical analysis. The data were analyzed using SPSS Statistics version 17. Results are presented as means \pm SD. Differences in continuous variables were analyzed by the unpaired t -test. Differences between categorical variables were assessed using the χ^2 test. Backward stepwise multiple regression was performed to determine independent predictors of BAT detectability. Odds ratio and confidence intervals were determined by multinomial logistic regression. $P < 0.05$ was considered statistically significant.

RESULTS

Distribution of BAT. BAT was most commonly located in the supraclavicular fossae (60.4%), followed by the posterior cervical (58.1%) areas. Less common locations were in the vicinity of the costovertebral junctions (37.6%), the superior mediastinum (19.1%), and the axillae (8.9%) (Fig. 2). We rarely detected BAT in the region of the crus of diaphragm, epigastrium, and atrial appendage (1%).

Histological confirmation of the presence of BAT. Fat biopsy from PET-positive fat showed cells with multilobulated lipid droplets (Fig. 3A), strongly positive for UCP1 (Fig. 3B), characteristic of BAT. Adjacent subcutaneous fat revealed cells with unilocular lipid droplets (Fig. 3C), characteristic of WAT. UCP1 staining was absent (Fig. 3D).

Reproducibility. Among patients with PET-CT evidence of BAT, we identified a total of 145 who were scanned more than once. To assess scan-rescan reproducibility, we determined the likelihood of one additional scan being positive among those patients with BAT. Among patients who had more than two scans, the frequency of another scan being positive increased with increasing occasions of study (Fig. 4): 8% in those studied twice, 18% in those studied three times, 50% in those studied four times, and 65% in those studied more than four times. We calculated the probability of detecting a positive scan among patients with BAT by dividing the total number of observed positive scans by the total number of expected positive scans. For example, among 60 patients who had two studies, only five positive scans were observed against an expected positive total of 60, returning a probability of 8.3%. The probability of detecting another positive scan for those who were studied three, four, five, six, and seven times were 9.0, 24, 6.7, 12.7,

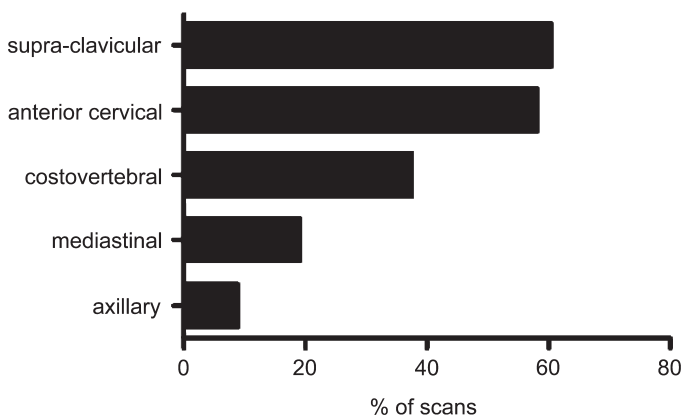


Fig. 2. Anatomic distribution of brown adipose tissue (BAT) obtained from 250 patients.

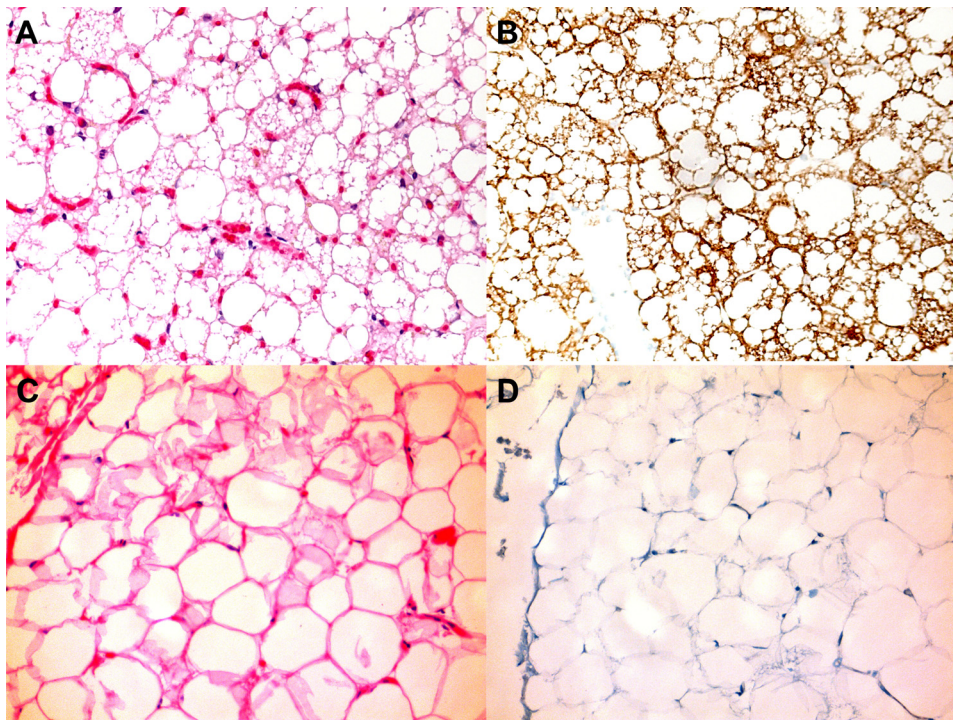


Fig. 3. Histological characteristics of PET-positive fat ($\times 40$) in a 19-yr-old woman. Sections of PET-positive fat (A) showed adipocytes with multilobulated lipid droplets (hematoxylin and eosin) stained strongly for UCP1 (B). Adjacent subcutaneous fat showed adipocytes with unilobulated lipid droplets (C) negative for UCP1 (D).

and 18.8%, respectively. From the collective studies of multiple scans, the average probability of obtaining another positive scan among patients with BAT is 13.3%. Standard PET-CT is therefore poorly reproducible and insensitive for BAT detection.

Prevalence. BAT was detected in 250 of 2,934 patients, yielding an apparent prevalence of 8.5%. The reproducibility estimation indicates that among patients who harbored BAT, the chance of detecting another positive scan is only 13.3%. In other words, only one in eight patients with BAT will have a positive scan when scanned on an additional occasion. On the basis of this probability, we estimated that the true prevalence of BAT is 64%, nearly eight times higher than the apparent estimate derived from a single study.

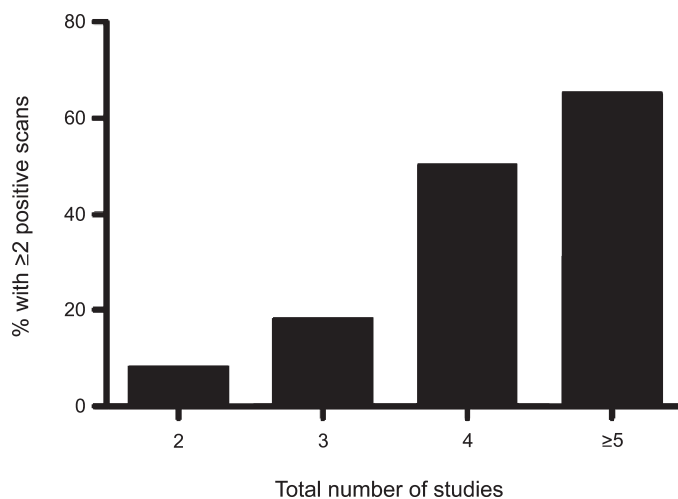


Fig. 4. Percentage of patients with at least two positive scans among those who had had multiple PET-CT and at least one positive scan.

Factors associated with BAT. Across the 2,934 patients, age, BMI, and fasting glucose levels were significantly lower in the group with a positive scan compared with the group with negative scans (Table 1). The presence of BAT was associated with female sex, younger age, lower BMI, and lower fasting glucose levels. The odds ratio for the detection of BAT ranged from 4.17 for female sex to 1.6 for lower fasting glucose level. In a multivariate analysis, all independent variables, except fasting glucose, were significantly associated with the presence of BAT (Table 2).

Among the 145 patients who had multiple scans (mean scanning interval 7.2 ± 1.1 mo), the factors associated with BAT detectability were mean body weight (54.9 ± 0.5 vs. 58.2 ± 0.8 kg, $P < 0.001$) and fasting glucose (4.9 ± 0.3 vs. 5.5 ± 0.3 mmol/l, $P = 0.03$), which were significantly lower on the occasions when BAT was detected. Mean maximum outdoor temperature was not significantly different on occasions when PET-CT was positive and negative [19.8 ± 1.8 vs. $20.4 \pm 2.1^\circ\text{C}$, $P = \text{not significant (NS)}$]. Figure 5 shows a patient who was scanned twice under the same conditions, where PET-CT was positive on the first occasion but not the second. Body weight (55 vs. 62 kg) and fasting glucose (4.2 vs. 5.9 mmol/l)

Table 1. Comparison of characteristics between patients with positive PET-CT scans and those with negative scans

| | Patients With Positive Scans | Patients With Negative Scans | P Value |
|------------------------------------|------------------------------|------------------------------|---------|
| n | 250 | 2,684 | |
| Sex, %female | 73 | 57 | <0.001 |
| Age, yr | 36 ± 1 | 52 ± 1 | <0.001 |
| Body mass index, kg/m ² | 20.1 ± 0.1 | 24.9 ± 0.1 | <0.01 |
| Fasting glucose, mmol/l | 4.9 ± 0.1 | 5.5 ± 0.1 | <0.01 |

Data are means \pm SE.

Table 2. *Univariate and multivariate analyses of factors associated with positive PET-CT scans*

| Variable | Univariate | | Multivariate | |
|------------------------------------------------------|---------------------|---------|---------------------|---------|
| | Odds Ratio (95% CI) | P Value | Odds Ratio (95% CI) | P Value |
| Sex | 4.2 (3.0–5.7) | <0.001 | 3.2 (2.3–4.4) | <0.001 |
| Female vs. male | | | | |
| Age, <50 vs. >50 yr | 2.0 (1.5–2.6) | <0.001 | 1.6 (1.2–2.1) | <0.001 |
| Body mass index, kg/m ² , <22.5 vs. >22.5 | 3.8 (2.9–5.3) | <0.001 | 2.8 (2.1–3.8) | <0.001 |
| Fasting glucose, mmol/l, <5.3 vs. >5.3 | 1.6 (1.2–2.2) | 0.002 | 1.3 (1.0–1.8) | 0.1 |

CI, 95% confidence interval.

were lower when the scan was positive. Maximum outdoor temperatures were similar on the two occasions (23.7 vs. 21.4°C).

For each PET-CT scan, an assessment was made of the presence of malignancy on the basis of FDG uptake. BAT was found in 50% of the scans with evidence of active malignancy compared with 44% of the scans where there was no PET-CT evidence of active disease ($P = \text{NS}$). Therefore, BAT was not associated with the presence or absence of malignant disease as detected by PET-CT.

DISCUSSION

In this review of 4,834 FDG-PET-CT scans in 2,934 patients, we report three important findings. First, reproducibility of PET-CT for BAT detection is low under standard conditions. Second, BAT is present in most adult humans, with a prevalence higher than previously published estimates based on single studies in similar cohort of adult humans. Third, BAT is strongly and inversely related to body weight and blood glucose, not only between individuals but also within individuals scanned on different occasions.

There is uncertainty in the literature on the prevalence of BAT in adult humans. Retrospective series based on PET-CT data report a prevalence of 5–10% in ambient scanning conditions (2, 5–7, 12, 17, 25). Our findings provide strong evidence that this is likely to be a gross underestimate, as reproducibility and sensitivity were not systematically examined in any of the studies. Rousseau et al. (18) found that PET scanning was consistently negative for BAT in only 6 of 33 women who were scanned five times and only one woman was positive for BAT on all five occasions. Our criteria for PET-CT positivity are stringent, and a false positive is highly unlikely. This is supported by the confirmation of the presence of BAT histologically in PET-positive fat (Fig. 3). Our systematic evaluation of scan-rescan reproducibility in a large cohort of patients indicate that among patients with BAT, an additional PET-CT study was positive in only 13.3% of cases. In the present study, BAT was detected in only 8.5% of patients studied once. However, extrapolation based on the low reproducibility would indicate that the true prevalence in our study cohort is 64%, nearly eight times higher. This mathematical calculation challenges the validity of the apparent low prevalence of BAT previously reported from similar studies. Our contention is strongly supported by a recent study in 25 healthy men, where 24 of the 25 (96%) individuals returned a positive PET-CT when cold-exposed to a temperature at 16°C (21),

conditions that stimulate BAT activity (4). Our findings indicate that estimates of prevalence, based on a single scan where the ambient temperature was not optimized for BAT detection, are likely to underestimate the true prevalence.

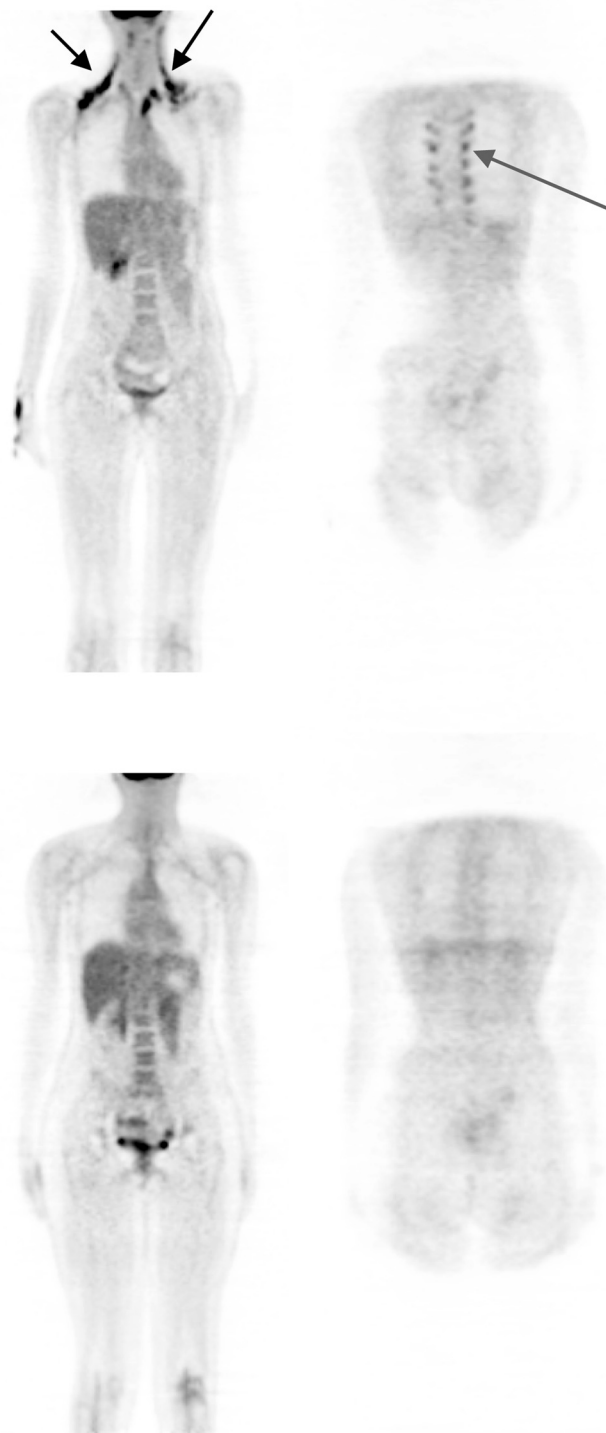


Fig. 5. Coronal PET-CT scans in an 18-yr-old woman performed 6 mo apart. First scan (top) shows increased FDG uptake in both supraclavicular fossae, neck, superior mediastinum (black arrows), and the costovertebral junctions posteriorly (gray arrows). The second study (bottom) shows normal glucose metabolism in the region examined and absent brown fat FDG uptake.

Previous studies have observed that body weight and glucose level are lower in subjects with BAT than in those without, which hints at the metabolic importance of BAT (7, 17, 19). We also observed a similar metabolic relationship of lower body weight and glucose levels in patients with PET-CT positive for BAT in the present study. However, in the group that was studied on multiple occasions, we also observed a similar relationship within the same individual. Body weight and glucose level were 6 and 10% lower, respectively, on occasions when PET was positive. The finding of such a relationship within a selected group of patients with BAT provides additional evidence that BAT activity is metabolically significant. This relationship is not accounted for by environmental temperature differences. It highlights that acute rather than chronic temperature changes, as shown in cold stimulation studies (21), may be more important in regulating BAT activity in today's very well-insulated humans, who generally maintain thermoneutrality at all times. Other investigators have linked BAT activity to weight loss in the pathogenesis of cancer-induced cachexia (3, 20). It is possible that BAT activity was linked to tumor recurrence or cachexia; however, we did not find a greater tumor activity on occasions when PET was positive.

We appreciate that there are several limitations in our study. It is retrospective, so we cannot be certain whether the association between BAT and an improved metabolic profile represents a cause or an effect relationship. However, as the thermogenic capacity of BAT is dependent on the oxidative metabolism of glucose and fatty acids, it is conceivable that the lower fasting glucose and BMI among patients with positive PET-CT scans are a metabolic consequence of BAT activity, and if so, this may contribute to an important proportion of total daily energy expenditure (EE). This has important clinical implications, as physical activity represents a diminishing fraction of total EE in contemporary sedentary society. The AustDiab Study has revealed that over 90% of waking hours is spent in sedentary or light-intensity activity (10). Thus, resting EE is becoming the principal component of total EE and enhancing resting EE through stimulation of BAT activity may have far reaching benefits.

We suggest that our results provide evidence to support a significant metabolic role for BAT. Should our findings be dismissed because our population has an underlying malignancy? We offer that, although extrapolation of our findings to the general population should be done cautiously, it is nevertheless appropriate. It is unlikely that PET-CT evaluation in large cohorts of healthy adults can be performed because of the cost and radiation exposure.

In summary, our study reveals that BAT is present in nearly two-thirds of adult humans. Standard PET-CT has a 13% detection probability for BAT. BAT is detected more frequently in women and young adults. BAT is more frequently detected when body weight and glucose levels are lower. We conclude that BAT is present in most adult humans. PET-CT is an insensitive and poorly reproducible method so that the detection of BAT will be missed in the vast majority of humans. Single PET-CT evaluations are of limited utility in the investigation of BAT physiology in humans. The inverse relationship to body weight and glucose levels suggests a significant role in metabolism and energy homeostasis in adult

humans. Strategies to stimulate BAT activity may be a promising approach to manage obesity.

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DISCLOSURES

No conflicts of interest are reported by the authors.

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