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Original Article

Effect of brown adipose tissue activation on myocardial fluorine-18-fluorodeoxyglucose uptake

ABSTRACT

The aim of this study is to investigate the relationship between brown adipose tissue (BAT) activation and myocardial fluorine-18-fluorodeoxyglucose ([^{18}F] FDG) uptake in terms of intensity and patterns. The patients were divided into two groups as follows: BAT and control groups. The BAT group consists of 34 cases that showed BAT uptake. The control group, with no BAT uptake, included 68 patients who were matched for body mass index, gender, and season. The scans were retrospectively reviewed by two nuclear medicine physicians who visually evaluated the intensity of myocardial [^{18}F] FDG uptake. The myocardial [^{18}F] FDG uptake was visually classified into the following three patterns: diffuse, heterogeneous, and focal. The regions of activated BAT distribution were noted. The mean myocardial [^{18}F] FDG uptake was 2.50 ± 0.75 for the BAT group and 2.13 ± 0.88 for the control group with a statistically significant difference (P = 0.031). The myocardial [^{18}F] FDG uptake pattern was similar in the BAT and control groups with the diffuse pattern being the most common, followed by the heterogeneous and less commonly focal. In the BAT group, the anatomical distribution of BAT was mainly in supraclavicular, paravertebral, and axillary and to a lesser extent in cervical regions. BAT group had a significantly higher intensity of [^{18}F] FDG myocardial uptake compared to that of the control group. The presence of activated BAT did not affect the pattern of myocardial uptake. Knowledge of these findings may help in understanding the variability of myocardial [^{18}F] FDG uptake and consequently in avoiding misinterpretation of cardiac findings in positron-emission tomography/computed tomography studies.

Keywords: Activated brown adipose fat, fluorine-18-fluorodeoxyglucose, myocardial uptake

INTRODUCTION

Adipose tissue has an important effect on human health as it plays a significant role in energy balance. There are two types of adipose tissue in the human body as follows: white adipose tissue (WAT) and brown adipose tissue (BAT). These two types have different physiological functions. WAT serves as an insulator and stores energy. On the other hand, BAT generates energy due to the abundance of mitochondria.

It has been conventionally believed that BAT only exists in infants and disappears after a few years of life.[1] Such a conclusion was derived from studying the distribution of BAT in rats and comparing it to humans. As the perinephric area is the main site of BAT in rats, it was assumed to be the same in humans. Therefore, most of the studies on BAT distribution in humans focused mainly on the perinephric area, where it was concluded that BAT disappears after a few years of life.[2]

Shortly, after the introduction of fluorine-18-fluorodeoxyglucose ([^{18}F] FDG) positron-emission tomography combined with computed tomography (PET/CT) in clinical practice, it was noted that BAT is present in adult humans and

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can be imaged due to its metabolic activity and ability to take up [^{18}F] FDG.[3] Based on the pattern of [^{18}F] FDG uptake, it was observed that the supraclavicular area is the main site of BAT distribution in adult humans rather than the perinephric area. It was also noted that BAT can also be found at multiple other areas, including the neck, axilla, paravertebral, mediastinal, perinephric, and pericrural areas. Following this interesting observation, it was concluded that BAT persists for a longer period in humans than previously assumed.[4]

Several factors play a role in activating BAT and therefore, increasing its FDG uptake. BAT activation is regulated by the sympathetic noradrenergic nerves that are richly found in this tissue.[5-7] BAT is activated in response to acute cold weather exposure or by ingestion of certain food ingredients such as capsaicin and capsinoids to produce heat and contribute to thermogenesis.[5,8,9]

These physiological changes that are associated with the cold-induced sympathetic stimulation are not confined to BAT and may also affect other organs in the body, including the heart.[10] Multiple previous reports stated that myocardial [^{18}F] FDG uptake showed various physiological patterns.[11] The aim of this retrospective study is to explore the possible relationship between BAT activation and myocardial [^{18}F] FDG uptake as well as to investigate the intensity and patterns of myocardial [^{18}F] FDG uptake.

METHODOLOGY

Patient population

This is a retrospective analysis of [^{18}F] FDG PET/CT studies performed for oncological indications between 2011 and 2013. The cases were divided into two groups as follows: BAT and control group. The BAT group consists of 34 cases that showed BAT uptake and included 14 males and 20 females with age ranging from 22 to 84 years (mean of 49.6 ± 16.2 years). The control group, with no BAT visualization, included 68 patients, 28 males and 40 females, with age ranging from 29 to 88 years (mean age of 61.3 ± 12.7 years). The control group consists of two patients without BAT uptake for each BAT patient. The control and BAT patients were matched for body mass index (BMI), gender, and season of the study. The patients' characteristics were reviewed and the BMI was calculated [Table 1].

Table 1: Brown adipose fat and control patients' demographic data

	Brown fat patients	Control patients
Gender, *n* (%)		
Female	20 (58.8)	40 (58.8)
Male	14 (41.2)	28 (41.2)
Age (years)		
Mean±SD	49.6±16.2	61.3±12.7
Median (range)	51.0 (22.0-84.0)	61.5 (29.0-88.0)
Race, *n* (%)		
White	28 (82.4)	56 (82.4)
Black	6 (17.6)	12 (17.6)
BMI (kg/m^2)		
Mean±SD	27.0±6.6	27.2±6.7
Median (range)	26.0 (17.6-42.6)	25.9 (16.1-43.7)
Weight (kg)		
Mean±SD	77.7±20.8	78.2±22.8
Median (range)	74.0 (49.0-130.0)	75.5 (45.0-149.0)
Height (m)		
Mean±SD	1.7±0.1	1.7±0.1
Median (range)	1.7 (1.5-1.9)	1.7 (1.5-1.9)

SD: Standard deviation; BMI: Body mass index

Image acquisition

All patients have fasted for 4–6 h, and their blood glucose level was <200 mg/dL (11.1 mmol/L). An intravenous injection of 5.18 MBq/kg (0.14 mCi/kg) of [^{18}F] FDG was administered, and the imaging started after an uptake period of 60 min. All scans were acquired using a PET/CT scanner (Gemini TF-64 slice CT-Philips Medical Systems). Emission data were acquired on an average for 20–21-bed positions (193 cm coverage, identical to the CT protocol). Emission scans were acquired at 1–2 min per bed position. The field of view (FOV) was from head to toe in all patients. The three-dimensional (3D) whole-body acquisition parameters consisted of a 128 × 128 matrix and an 18 cm FOV with a 50% overlap. Processing consisted of the 3D row-action maximum likelihood algorithm method.[12] The attenuation-corrected PET images, nonattenuation-corrected PET images, and CT images were all reviewed.

Data analysis

The scans were retrospectively reviewed by two board-certified nuclear medicine physicians independently. The intensity of myocardial [^{18}F] FDG uptake was evaluated visually for all the scans. The intensity of myocardial uptake was sorted into 0 (no uptake), 1 (mild uptake that is less than blood pool), 2 (moderate uptake that is equal to blood pool), and 3 (intense uptake that is more than blood pool) [Figure 1]. In addition, the regions of the activated brown fat distribution were noted.

The myocardial [^{18}F] FDG uptake was visually classified into three patterns: diffuse, heterogeneous, and focal. The diffuse pattern indicates homogeneous uptake of [^{18}F] FDG throughout the left ventricle (LV) wall. The heterogeneous pattern indicates patchy uptake within the LV wall. The focal pattern indicates a localized area of uptake within the LV wall.

Statistical analysis

IBM Statistical Package for Social Sciences version 25 computer program (SPSS-Inc., Chicago, IL, USA) was used

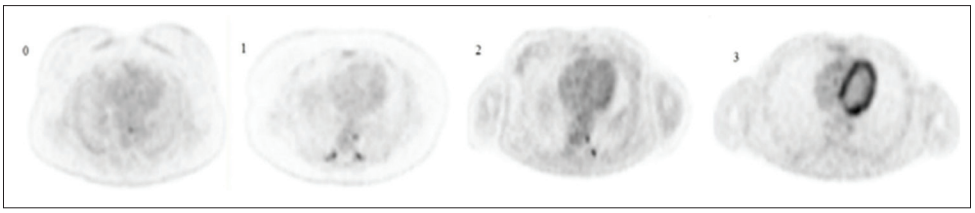

Figure 1: Intensity of myocardial uptake: 0: No uptake; 1: Mild; 2: Moderate; 3: Intense

to perform all groups' comparison statistical analysis. Group statistics providing basic information about group comparisons, including the sample size (*n*), mean, and standard deviation (SD), were calculated and presented as mean ± SD. The independent samples *t*-test was conducted to compare the means of two independent groups (BAT vs. control) to determine the statistical significance.

RESULTS

There was no statistically significant difference in the gender, race, BMI, weight, and height of participants between the BAT and control group [Table 1]. However, there was a statistically significant difference (*P* 0.003) in age between the two groups with the BAT group being younger. Among the BAT group, 14.7% had mild, 20.6% had moderate, and 64.7% had intense myocardial [^{18}F] FDG uptake [Table 2]. On the other hand, 32.4% of the control group had mild myocardial uptake of [^{18}F] FDG, 22.1% had moderate uptake, and 45.5% had intense uptake [Table 2]. The mean myocardial [^{18}F] FDG uptake was 2.50 ± 0.75 for the BAT group and 2.13 ± 0.88 for the control group with a statistically significant difference ($P = 0.031$) [Table 3].

In the BAT group, the anatomical distribution of BAT was mainly in supraclavicular, paravertebral, and axillary and to a lesser extent in cervical regions. There was one case at each of the mediastinal, suprarenal, and perinephric regions [Table 4]. The myocardial [^{18}F] FDG uptake pattern in the BAT group was focal in 3%, heterogeneous in 17%, and diffuse in 80% of patients [Figure 2]. On the other hand, the uptake pattern in the control group was focal in 5%, heterogeneous in 18%, and diffuse in 78% of patients [Table 5].

DISCUSSION

The normal myocardium is capable of oxidizing multiple metabolic substrates, including free fatty acids, glucose, and lactate.[13] Several factors, including myocardial blood flow and hormones, determine the proportion of substrates used by the myocardium under different conditions.[14] Under fasting conditions, myocardial glucose metabolism decreases because of the fall in plasma insulin level and the reduction of glucose transport into the myocytes.[13] When [^{18}F] FDG

Table 2: Intensity of fluorine-18-fluorodeoxyglucose myocardial uptake

Myocardial uptake intensity	Control (%)	BAT (%)
1	22 (32.4)	5 (14.7)
2	15 (22.1)	7 (20.6)
3	31 (45.5)	22 (64.7)

BAT: Brown adipose tissue

Table 3: Mean fluorine-18-fluorodeoxyglucose myocardial uptake in brown adipose fat and control groups

Group	Subject#	Myocardial uptake (mean)	*P*
Control	68	2.13±0.88	0.031
BAT	34	2.50±0.75	

BAT: Brown adipose tissue

Table 4: Pattern of activated brown adipose fat distribution

BAT location	Percentage of occurrence
Supraclavicular	34
Paravertebral	23
Axillary	22
Cervical	12
Mediastinal	3
Suprarenal	3
Perinephric	3

BAT: Brown adipose tissue

Table 5: Pattern of fluorine-18-fluorodeoxyglucose myocardial uptake in brown adipose fat and control groups

Pattern of [^{18}F] FDG cardiac uptake	Control (%)	BAT (%)
Focal	5	3
Diffuse	78	80
Heterogeneous	18	17

[^{18}F] FDG: Fluorine-18-fluorodeoxyglucose; BAT: Brown adipose tissue

PET/CT studies are performed for oncological indications, the patients are routinely asked to fast for 4–6 h. Under this condition, myocardial [^{18}F] FDG uptake is usually variable and nonuniform, and therefore, the heart is not routinely evaluated during the interpretation of these studies.[15]

The results of this study show a significantly higher myocardial [^{18}F] FDG uptake in the group of patients with activated BAT in comparison to the control group. This increase in myocardial [^{18}F] FDG uptake could be attributed to the sympathetic nervous system stimulation, as both the heart and BAT are densely innervated by the sympathetic

adrenergic nerves. This association can be explained by multiple underlying mechanisms. The sympathetic nerve terminals, in response to cold weather exposure, release noradrenaline that binds to B-adrenergic receptors and initiates a cascade of intracellular events leading to the hydrolysis of triglycerides and the release of fatty acids. The fatty acids activate uncoupling protein-1 that is selectively expressed in BAT, resulting in the uncoupling of oxidative phosphorylation from adenosine triphosphate synthesis and the release of energy as heat.[6] In addition, sympathetic signaling upregulates the expression of glucose transporter 4 in the myocardium, as well as in fatty tissues and muscles, resulting in an influx of glucose and [^{18}F] FDG into the cells with sympathetic stimulation.[1] Hintsala demonstrated that cold exposure increases sympathetic activity and cardiac work that is manifested by increased peripheral blood pressure and heart rate.[16]

Multiple other factors may be involved in determining [^{18}F] FDG uptake in the heart. In a study conducted by Vosselman *et al*., [^{18}F] FDG uptake in BAT was measured after the administration of the nonselective B-agonist isoprenaline (ISO).[17] Despite the observed increase in the HR and energy expenditure, the results did not show BAT activation with ISO. However, simultaneous administration of ISO and acipimox, which inhibits lipolysis and lowers fatty acids, resulted in increased [^{18}F] FDG uptake in the heart but not in BAT. They concluded that fatty acids competed with [^{18}F] FDG uptake in the heart and that systemic nonselective B-adrenergic stimulation did not activate BAT. Another study by Söderlund found a significant reduction of [^{18}F] FDG uptake in the BAT after pretreatment with propranolol.[18] They also noted a decrease in myocardial [^{18}F] FDG uptake following the pretreatment with propranolol, although there was no statistical significance. On the other hand, Lindholm *et al*. found a mild increase in myocardial uptake after the administration of propranolol that also was not statistically significant.[19]

Our results show that metabolically active BAT was most commonly found in the supraclavicular, axillary, cervical, and paravertebral regions [Figure 3]. It occurred less commonly in the mediastinal, suprarenal, and perinephric regions. These findings are consistent with previously published data by Cronin *et al*. which stated that metabolically active BAT was mostly localized in the neck and supraclavicular region (51.7%)

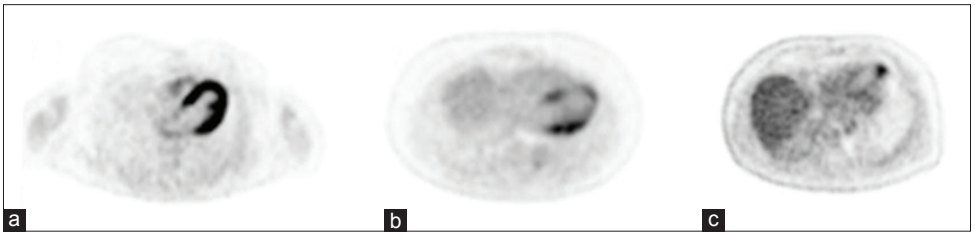

Figure 2: Patterns of myocardial uptake. (a) Diffuse. (b) Heterogeneous. (c) Focal

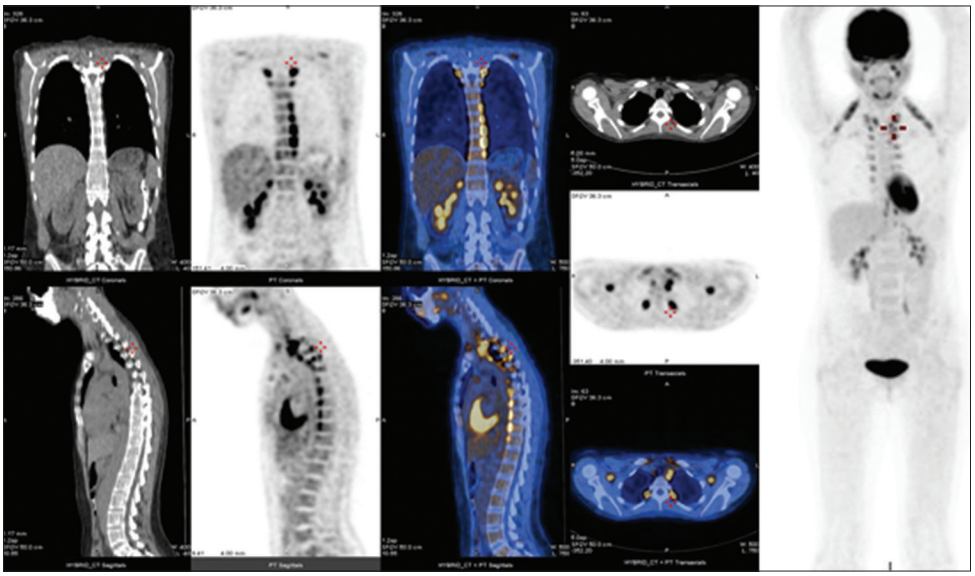

Figure 3: Maximum intensity projection, axial, coronal and sagittal images of fluorodeoxyglucose positron-emission tomography/computed tomography study of a 30-year-old female with Hodgkin's lymphoma showing activated supraclavicular and paravertebral brown adipose tissue with diffuse intense myocardial uptake

and to a lesser extent in the mediastinum (5.7%).[20] Multiple other studies are also consistent with our findings in that activated BAT is most commonly seen in the supraclavicular region.[21-23]

The prevalence of BAT and certain demographic data such as gender, age, BMI, and race were analyzed [Table 1]. In keeping with the published literature,[20-23] we found a higher prevalence of activated BAT in females (58.8%) as compared to males (41.2%). Cronin *et al*. reported that in their studied group, younger patients had more brown fat FDG uptake.[20] In terms of age, activated BAT was more commonly noted in our younger patients with a mean age of 49.6 years compared to the control group with a mean age of 61.3 years. The mean BMI in the activated BAT group was 27 indicating borderline overweight patients. In the published literature, the mean BMI of patients with BAT was more on the higher end of the normal range, around 25, which is similar to our results.[20,21]

Multiple studies reported that there is a large variability in the temporal and spatial myocardial [^{18}F] FDG uptake. Inglese *et al*. studied the myocardial patterns in 49 cancer patients free of cardiac diseases and found extremely large variability of the heart metabolic pattern.[24] Thut *et al*. found no reproducibility in myocardial uptake in serial [^{18}F] FDG PET scans in the same patients. They found no correlation in regional myocardial pattern and peak uptake of glucose with the length of fasting, gender, age, or cardiac risk factors.[25] Tiwari and Kand had visually classified the degree of myocardial FDG uptake in 91 cancer patients into no uptake, mild, moderate, and marked uptake.[26] They concluded that the degree of uptake is not significantly correlated with fasting blood sugar level, fasting period, or the age of the patient. In another study, Fallahi *et al*. reported that low-carbohydrate, high-fat diet for 24 h before imaging can suppress myocardial [^{18}F] FDG uptake, and they consider it as the only controllable independent factor affecting the intensity and pattern of myocardial uptake.[27] Another study by Nose *et al*. included 188 patients with no heart disease where they classified the myocardial uptake patterns into none, diffuse, focal, or focal on diffuse.[11] They concluded that physiological myocardial uptake has different patterns with the diffuse pattern being the most common (33.5%). Our results show that the diffuse myocardial uptake pattern is the most common pattern in both the control and BAT groups, which is consistent with the previous report. Our results also indicate that there is no statistically significant difference in the pattern of uptake between the BAT and the control groups. This may indicate that BAT activation does not influence the myocardial uptake pattern, which is the opposite of what was observed in the myocardial uptake intensity.

The present study is a retrospective study and was carried out in a single institution at a relatively warm country which may have lowered the prevalence of BAT in our patients. In addition, cancer or cancer therapy may affect BAT. Cases included in this study were selected from the same patient population; therefore, the potential for this to be a confounding factor should be balanced between the BAT and the control groups. Furthermore, matching between BAT and control groups was done for BMI/gender/season; however, the mean age in our BAT was younger than that of the control group (mean age 49.6 vs. 61.3, respectively). Future studies would be needed to validate our conclusion in a prospective multicenter study with larger sample size and a better age-matched BAT and control groups.

CONCLUSION

Patients with activated BAT who underwent [^{18}F] FDG PET/CT for oncological reasons had a significantly higher intensity of [^{18}F] FDG myocardial uptake compared to that of the nonactivated BAT patients. The presence of activated BAT does not affect the pattern of myocardial uptake. Knowledge of these findings may help in understanding the variability of myocardial [^{18}F] FDG uptake and consequently in avoiding misinterpretation of cardiac findings in PET/CT studies. It also adds to the knowledge of the sympathetic activation mechanism and its impact on myocardial FDG uptake.

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Conflicts of interest
There are no conflicts of interest.

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