Evaluation of ^{18}F -FDG Uptake Pattern in Brown Adipose Tissue Over Extended Time Period as Assessed by Multiple Time Point ^{18}F -FDG-PET

Trupti Upadhye · Arun Gandhi · Sandip Basu

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Abstract

Purpose To study the ^{18}F -FDG uptake pattern in brown adipose tissue (BAT) over an extended time period, by multiple-time-point fluorodeoxyglucose positron emission tomography (FDG-PET) imaging. The primary objective for this kind of research was that it could form a basis and may have further implications for obesity research, metabolic diseases and for cachexia of both malignant and benign origin.

Methods A total of 12 patients who had undergone routine FDG-PET for disease evaluation and had demonstrated prominent BAT uptake in their baseline scans were selected. The patients with the diagnosis of neuroendocrine tumors were excluded. Maximum standardized uptake values (SUVmax) were calculated in the BAT of the supraclavicular and paravertebral areas of either side, and were analyzed separately to examine their behavior individually. Time activity curves (TACs) were generated for [A] BAT SUVmax values and [B] SUVmax ratio of BAT/lung (B/L SUVmax ratio) at various time points.

Results Ten out of the 12 patients were imaged at four time points, and two patients were imaged for two time points. Amongst a total of $n=30$ sites, 23 were imaged at four time points and seven were imaged at two time points. Seventeen out of 30 area sites (56.67 %) demonstrated a peak value at 60 min and a falling trend of SUVmax afterwards; the

remaining showed a peak uptake value between 85 and 300 min after the first scan (i.e. 145–360 min after injection), and falling values thereafter. With regard to the B/L SUVmax ratio, ten out of 30 sites (33.33 %) demonstrated peak uptake at 60 min, and the remaining showed a rise, with peak uptake at times between 85 and 300 min after the first scan (i.e. 145–360 min after injection) and falling values thereafter. No additional area of BAT uptake was observed over the extended time period in this study.

Conclusion Wide variability was observed in the BAT FDG uptake over an extended period of time. Nearly half of the sites demonstrated an increase in FDG uptake until 360 min (i.e. 6 h) after injection, while the remaining half showed peak uptake at 1 h and subsequent fall of uptake. In the future, it will be worthwhile to study whether there exists any difference in time course of FDG uptake in brown fat between patients with cancer and those scanned for benign etiologies, or between obese and non-obese individuals.

Keywords FDG-PET · Brown adipose tissue · Multiple time point studies · Brown fat

Introduction

The occurrence of functional brown adipose tissue (BAT) was an important observation after ^{18}F -fluorodeoxyglucose positron emission tomography (^{18}F -FDG-PET) was routinely employed in clinical practice. It is a known fact that uptake of ^{18}F -FDG continues to increase in tumors with time and does not reach the peak until several hours after ^{18}F -FDG injection. In a previous report, it was concluded that on dual-time-point scanning, there is a progressive

T. Upadhye · A. Gandhi · S. Basu (✉)
Radiation Medicine Centre, Bhabha Atomic Research Centre
(BARC), Tata Memorial Hospital Annexe,
Jerbai Wadia Road, Parel,
Bombay 400 012, India
e-mail: drsanb@yahoo.com

Table 1 Detailed patient characteristics included in the study

No.	Age	Sex	CASE	BMI
1	17	F	Embryonal Rhabdomyosarcoma (ERMS) vagina	16.63
2	20	M	Primitive Neuroectodermal Tumor (PNET) humerus	23
3	46	F	Ca Cervix	28.2
4	24	M	Burkitts lymphoma	19.27
5	23	M	Hodgkins Disease	15.625
6	25	M	Ewings Femur	25.26
7	13	M	Hodgkins Disease	20.27
8	22	M	Anaplastic Ca	21.22
9	14	M	Ewings sarcoma	17.8
10	11	F	Hodgkins Disease	16.63
11	12	M	Hodgkins disease	15.9
12	30	M	Non Seminomatous Germ Cell Tumor (NSGCT)	19.6

increase in FDG uptake within most of the hypermetabolic brown fat areas, although this can have wide variability in distribution and degree of ^{18}F -FDG uptake [1]. In addition to this, in some instances, there was an increase in the number of brown fat spots on the second-time images [1].

We endeavored in this study, to estimate ^{18}F -FDG uptake in BAT over an extended period of time in a prospective setting. We believed that studying the nature of ^{18}F -FDG uptake with time will be an important addition to the study of BAT physiology on glucose metabolism, and may have important implications for various conditions, like obesity research, metabolic diseases and for cancer induced cachexia. Also, this information might prove useful when there is difficulty in differentiating BAT from a suspicious malignant

lesion, and dual time point ^{18}F -FDG-PET is being undertaken to address this in a clinical PET study.

The usual sites of BAT depots, as revealed in clinical PET imaging, include: (a) supraclavicular area (popularly known as USA fat), (b) neck, (c) paravertebral depot, (d) mediastinal depot, (e) axillary depot, (f) infradiaphragmatic and perirenal depots. Both supraclavicular and neck depots are the most often occurring depots [2, 3]. The uptake is enhanced in Cushing's syndrome. The measures routinely employed for differentiating brown fat from malignant lesions are interventions such as propranolol, reserpine, diazepam, and fentanyl, and warming maneuvers. Localization by PET/computed tomography (CT) has also helped in differentiating BAT from the malignant lesions [2–4].

Table 2 SUVmax and SUVmax /right lung ratio in right supraclavicular BAT

No.	t=1	scl rt	scl rt/lung	t=2	scl rt	scl rt/lung	t=3	scl rt	scl rt/lung	t=4	scl rt	scl rt/lung
1	0	9.37	15.881	130	13.3595	15.181	204	10.34	18.333 3	350	10.497	14.419
2	0			120			150			360		
3	0	8.50278	9.762	100	12.3797	27.510	250	6.420	9.3185	500	6.099	6.354
4	0	17.7436	24.207	150	12.4346	17.764	410	11.633	15.286	470	10.237	15.749
5	0	15.0092	21.323	90	12.0178	25.851						
6	0	35.5327	71.875	110	32.8917	60.982	195	23.681	41.913	300	15.951	33.899
7	0	11.5916	12.995	86	8.01871	7.952	225	8.530	14.508	290	7.135	12.632
8	0			107								
9	0	22.7568	27.409	158	16.1054	26.477	240	11.744	22.797	285	12.604	20.505
10	0	19.1526	23.402	82	14.8677	20.181	145	11.313	30.682	210	8.960	23.128
11	0	4.28077	10.885	85	3.93699	12.598	160	3.904	11.551	200	3.833	11.521
12	0	4.60828	11.107	132	4.10066	12.746	216	3.684	6.200	313	2.957	4.2881

Scl supraclavicular area; rt right side; t time point number

Table 3 SUVmax and SUVmax /left lung ratio in left supraclavicular BAT

No.	t=1	scl lt	scl lt/lung	t=2	scl lt	scl lt/lung	t=3	scl lt	scl lt/lung	t=4	scl lt	scl lt/lung
1	0	5.987	8.857	130	7.05	8.598	204	5.4	8.238	350	5.4	8.194
2	0	11.01	21.173	120	10.678	20.147	150	10.969	8.466	360	9.386	8.105
3	0	9.09777	15.471	100	9.230	14.422	250	5.38	11.824	500	5.455	5.401
4	0	20.317	26.909	150	13.984	15.538	410	7.871	10.223	470	6.3	7.241
5	0	14.171	29.358	90	13.043	23.845						
6	0	31.876	45.092	110	34.789	60.903	195	22.652	33.311	300	15.535	32.085
7	0	11.533	16.168	86	12.255	22.536	225	7.817	15.666	290	7.019	15.812
8	0	5.117	6.839	107	5.993	13.038						
9	0	19.028	23.529	158	13.856	29.618	240	11.690	25.531	285	13.914	31.351
10	0	17.0748	18.460	82	14.036	24.994	145	11.242	22.998	210	9.334	26.026
11	0	4.7182	11.998	85	4.895	15.413	160	4.546	19.339	200	4.332	9.296
12	0	3.680	6.703	132	4.157	6.985	216	3.688	6.865	313	2.965	5.560

Scl supraclavicular area; *lt* left side; *t* time point number

Materials and Methods

Patient Population

Twelve patients (nine males, three females; mean age of 21 years, age range of 11–46 years, and mean body mass index [BMI] of 19), who had shown brown fat uptake in their baseline scans, were selected. The patients with the diagnosis of neuroendocrine tumors were excluded (due to the effect of these tumors on BAT FDG uptake). Since the patient group was of diverse pathologies, care was taken to avoid the BAT close to the primary malignancy. None of these patients fell into the obese category (none having BMI > 30). The detailed patient characteristics have been described in Table 1.

FDG-PET Imaging Protocol

All patients were injected with 10–15 mCi of ^{18}F -FDG intravenously. The patients were fasting for at least 6 h prior to the scan and were non-diabetic. PET images were acquired on a dedicated whole body full ring scanner (GE Advance System) in all patients. This dedicated PET Scanner of the ring detector

type, including 18 detector rings in 2D mode, had the following: 18 direct planes + 17 cross planes = 35 planes or slices per bed of the patient, with an overlap of one slice.

Ten of these patients were imaged at four time points, and two of them were imaged for two time points (due to patient's condition). While an endeavor was made to keep a uniformity of the time points, this was not possible, except for time point 1 (in view of a busy clinical setting and patients' conditions), and thus for each individual patient, the specific time for imaging was mentioned and the time activity curve (TAC) was generated accordingly. Sequential time point scans were acquired only in the area showing prominent BAT FDG uptake. Germanium source was used for attenuation correction. The images were reconstructed using an iterative algorithm (OSEM). Patients were allowed to have food after the first scan.

Study Analysis

Coronal slices were selected for drawing the region of interest (ROI). The number of ROIs drawn per patient depended upon the regions of brown fat showing FDG

Table 4 SUVmax and SUVmax /right lung ratio in right paravertebral BAT

No.	t=1	pvt suv max	pvt rt/lung	t=2	pvt suv max	pvt rt/lung	t=3	pvt suv max	pvt rt/lung	t=4	pvt suv max	pvt rt/lung
1	0	4.25	7.2034	130		0	204	4.778	8.472	350		0
3	0	6.63	7.6119	100	7.71	17.133	250	5.843	8.481	500	4.0221	4.190
5	0	10.06	14.288	90	8.237	17.719						
6	0	7.538	15.248	110	7.139	13.236	195	6.921	12.25	300	7.599	16.151

Pv paravertebral area; *rt* right side; *t* time point number

Table 5 SUVmax and SUVmax ratio of BAT/left lung in left paravertebral BAT

No.	t=1	pv lt suv max	pv lt/lung	t=2	pv lt suv max	pv lt/lung	t=3	pv lt suv max	pv lt/lung	t=4	pv lt suv max	pv lt/lung
4	0	10.97	14.526	150	9.911	11.012	410	4.52892	5.882	470	4.387	5.043
5	0	12.3356	25.555	90	10.22	18.678						
6	0	6.755	9.556	110	5.605	9.812	195	5.295	7.787	300	3.453	7.132
7	0	5.811	8.146	86	7.2913	13.409	225	5.5053	11.0339	290	4.025	9.067

Pv paravertebral area; lt left side, t, time point number

uptake on the first scan. There were some patients who showed uptake only in the supraclavicular area, whereas others also showed in other areas, such as the paravertebral area, hence the ROIs were variable in individual case scenarios. The SUVmax (lean body mass) was calculated in BAT of supraclavicular areas and Paravertebral areas for all the patients for all the time points. The SUVmax (LBM) is preferred to body weight, as the injected dose is corrected by the lean body mass, which makes the parameter more reliable. The areas showing maximum intensity were selected in such fashion that they were not close to the primary of the patient. The background regions were selected over the apical lung separately for both right and left areas at various time points. Lung FDG uptake was considered as a reference value, as this was the organ that was common to all images in all the time points (due to the usual locations of BAT). The measurements were made by an experienced nuclear medicine technologist with 8 years experience, under the supervision of an experienced nuclear medicine physician with more than 10 years of experience in the field. Both right and left supraclavicular and paravertebral areas were considered separately. The first time point ($t=1$) in this study (referred to as 0), was 60 min after injection of FDG.

To come to the conclusion that the uptake was indeed due to BAT, the typical pattern, which was clear in all the cases in our study population, was considered. Ancillary clinical data was also considered to rule out any disease pathology in the BAT regions.

Results

BAT in the supraclavicular areas on the right side was visualized in ten patients ($n=10$), out of which eight patients were imaged at four time points and two at two time points. Similarly, the left supraclavicular area was prominently visualized in 12 patients ($n=12$), out of which ten were imaged at four time points and two at two time points. The right paravertebral area was observed in four patients ($n=4$); two of these patients were imaged at four time points and two were imaged at two time points; the left paravertebral area was seen in a total of four patients ($n=4$), out of which three patients were imaged at four time points and one patient at two time points.

Thus, in a total of 30 sites, 23 patients were imaged at four time points and seven were imaged for two time points.

Fig. 1 Seven patients out of ten showed an initial peak value at 60 min and subsequent decrease in values of SUVmax with respect to time; three patients showed an increase in SUVmax with peak uptake in the time period from 100 to 225 min from the first scan, and a decrease thereafter (wherever the scans were acquired beyond this time)

Fig. 2 Three out of ten patients showed an initial peak value at 60 min and a decreasing trend in the SUVmax of right supraclavicular area/right lung values, and the remaining seven patients showed values that increased at time points from 85 to 225 min from the first scan and decreased thereafter

SUVmax was calculated over contiguous slices, and highest value was considered for analysis. Similar locations were used for placement of ROI in subsequent images. TACs were generated using SUVmax values and SUVmax of area/lung SUVmax (B/L SUVmax ratio) at various time points at which the scan was acquired [4].

The values obtained were then divided into two categories; one in which the peak uptake is at 60 min and falling thereafter; and the other, in which there is increase in uptake in subsequent images, peaking at 85–300 min after the first scan (145–360 min after injection of FDG), and falling after that.

The following site-specific classification was undertaken: (1) Supraclavicular area of the right side; (2) Supraclavicular area of the left side; (3) Para vertebral area of the right side; and (4) Para vertebral area of the left side.

The measured SUVmax values are depicted in Tables 2, 3, 4 and 5, and Figs. 1, 2, 3, 4, 5, 6, 7 and 8, with a clinical example (Fig. 9).

Discussion

The premise and the focus of this pilot study was to explore the dynamic pattern of BAT with FDG-PET, with a broader aim to initiate interest in such studies that would clarify behavior characteristics of BAT. A proper

understanding of BAT pathophysiology is hence essential, and has been briefed for better appreciation of the significance of this research study and its potential value for future studies in metabolism, obesity, etc. FDG uptake in the BAT was one of the important observations made when FDG-PET was introduced in clinical oncology practice. In a typical case, this was in the form of an intense, bilateral, symmetrically distributed, cold-induced uptake in few adults. This was important, as it was in contrast to the earlier belief that BAT was lost postnatally within the first few years, and that adult humans do not possess more than vestigial amounts of BAT. BAT activation in man has been proposed to be acutely cold-induced [5]. BAT is innervated by sympathetic nervous system and expresses β_1 , β_2 and β_3 adrenergic receptors, among which β_3 are predominant [6]. Physiologically, brown fat is stimulated by norepinephrine (NE) released from sympathetic nerves, leading to triglyceride breakdown. The resulting free fatty acids (FFA) are involved in the activation of brown-fat-specific uncoupling protein 1 (UCP1) or thermogenin. FFA is the main source of substrate combustion in mitochondria. Interestingly, in intact mice without UCP1, where NE is unable to stimulate any thermogenesis in brown fat cells, NE loses ability to increase glucose uptake. Therefore, it is assumed that thermogenin is a prerequisite for ^{18}F -FDG uptake in BAT in vivo. [7, 8]

Fig. 3 Five out of 12 patients showed an initial SUVmax peak value at 60 min, and thereafter followed a decreasing trend. Seven patients showed increase in SUVmax values, with peak value obtained at time points between 85 to 132 min from the first scan, and values decreased thereafter

Fig. 4 Five out of 12 patients showed an initial peak value at 60 min, followed by a decreasing trend in values of SUVmax of the left supraclavicular area/lung. The remaining patients showed an increase in value, peaking at around 86–285 min from the first scan, after which values showed a decreasing pattern

BAT is characterized by small cells, multilocularity, large numbers of mitochondria, increased vascularity and abundant sympathetic noradrenergic innervations, compared with widespread white adipose tissue (WAT) [9]. To avoid ^{18}F -FDG uptake in BAT, several interventions were used, but none of which gave 100 % results. Most popular among the interventions used is administration of Propranolol before the injection of ^{18}F -FDG. The other interventions that have been investigated with varying degrees of success include administration of reserpine, benzodiazepine and Fentanyl, warming maneuvers and localization by PET/CT [2, 10, 11]. Reserpine depletes stores of NE in nerve terminals at BAT. BAT has been reported to have benzodiazepine receptors to which diazepam binds as an agonist. In 1996, Barrington et al. reported that diazepam was useful in reducing symmetric “muscle” ^{18}F -FDG uptake in neck and paravertebral region of the thoracic spine.

Brown adipose tissue has significant potential in research related to obesity, and also it has been suggested as an explanation for cancer-induced cachexia. There have been reports of increasing or decreasing brown fat stores in these conditions [12–16]. We believe studying brown fat physiology with FDG-PET may have important implications for obesity research, metabolic disorders [13–15] and for cancer-induced cachexia.

In the population of patients examined in this study, we observed that 17 out of 30 areas (56.67 %) showed an initial peak of SUVmax at 60 min and a falling trend thereafter,

and the remaining areas that we considered showed a rise in SUVmax values, with peak obtained at times between 85 and 300 min after the first scan and falling thereafter, depending on whether a scan was acquired beyond that time. Ten out of the 30 areas (33.33 %) considered showed an initial peak at 60 min and a falling trend of B/L SUVmax ratio with respect to time, and the remaining areas showed a rise in values of B/L SUVmax ratio, with peak value at times between 85 and 300 mins after the first scan and falling thereafter, depending on whether the scan was acquired beyond that time. No additional areas of lesion were seen over the extended time period. The limitations of this study are (a) small sample size and (b) variation of time points amongst patients (due to a busy clinical setting and patients’ conditions). Thus, a further prospective study with strict protocol and with larger population would help in obtaining a more definitive conclusion. Another important aspect is that the hypermetabolic brown fat in the mediastinum and upper abdomen are more likely to be confused as primary malignancy or nodal metastases, because of the unusual location and frequent asymmetry. However, none of the 12 patients in the study population showed FDG uptake in these locations; it will, however, be worthwhile to study the usefulness of this methodology when such a situation is encountered.

From the above observations, it can be concluded that wide variability is observed in the FDG uptake pattern of BAT over an extended period of time, with nearly half of the sites demonstrating an increase in FDG uptake until 360 min

Fig. 5 One out of four patients showed a initial peak value at 60 min, and decrease in SUVmax value over a period of time; in three patients, there was an increase in the SUVmax values at around 100–300 min from the first scan, decreasing trend

Fig. 6 All four patients showed an increase in B/L SUVmax ratio from 90 to 300 mins from the first scan, with one patient showing a decrease in the value as it was acquired, until 500 min

Fig. 7 Three out of four patients showed a peak at 60 min, and a decreasing trend thereafter; one out of four patients showed an peak uptake at 86 min

Fig. 8 Two out of four patients showed a peak uptake at 60 min, followed by decrease in values, and two patients showed increase in values, with peak uptake at 86 min and 110 min from the first scan and then falling trend

Fig. 9 **a, b** and **c, d** FDG-PET studies in the same patient at multiple time points. Images in each panel have the time mentioned in minutes, with the first scan taken as $t=0$. Image at 500 min after first scan (i.e. 560 min after FDG injection) demonstrates significant reduction of FDG uptake compared to the initial three scans

(i.e. 6 h) after injection. It will now be worthwhile to study whether there exists any difference in time course of FDG uptake in brown fat between patients with cancer and those scanned for benign etiologies, between obese vs. non-obese

individuals, or how they vary with various pharmacological interventions.

Conflict of Interest The authors declare no conflict of interest.

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Sandip Basu: Study analysis, preparation of manuscript

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