Brown adipose tissue (BAT) activation at ^{18}F-FDG PET/CT: correlation with clinicopathological characteristics in breast cancer

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Abstract

Background: There is conflicting results of few published human ^{18}F-FDG PET/CT studies about BAT activation in breast cancer (BC). The aim of the study is to evaluate the association between the levels of BAT metabolic activity detected by ^{18}F-FDG PET/CT and clinicopathological characteristics of a tumor in patients with primary BC.

Results: BAT was activated in 16 out of 157 (10.2%) consecutive female patients with BC who underwent ^{18}F-FDG PET/CT for initial evaluation. The majority of patients (15/16) had bilateral uptake in the supraclavicular regions. The mean values of the highest SUVmax and total metabolic activity (TMA) of activated BAT were 13.3 ± 9.9 and 79.6 ± 45, respectively. Median outdoor temperature was significantly lower in the activated BAT group (P value=0.035). Patients with BAT activation tended to have a lower median primary tumor size and primary SUVmax, but not statistically significant than those without BAT activation. BAT activation was significantly more frequent among younger age groups (14/16) and patients with lower body mass index (BMI) (10/16), but it was insignificantly more frequent among estrogen receptor-positive (ER+), progesterone receptor-positive (PR+), human epidermal growth factor receptor2 negative (HER2-), invasive ductal carcinoma (IDC), grade II, luminal B subtype, high Ki-67 expression level, patients with positive nodal metastasis, and in patients without distant metastasis. TMA was significantly higher among HER2+ patients (P value=0.019), but insignificantly higher among the younger age groups, stages I and II, invasive lobular carcinoma (ILC), grade I, luminal B subtype, ER+, PR−, higher Ki-67 expression level, patients with positive nodal, and distant metastasis. BMI and patient's age were the significant independent predictor factors for BAT activation on multivariate regression analysis.

Conclusion: BAT activation in young age females is sex hormone-dependent, positively associated with less aggressive molecular subtypes of BC, less frequent in patients with distant metastasis. BAT activation may be a prognostic factor that carries a better prognosis in BC.

Keywords: ^{18}F-FDG PET/CT, Breast cancer, Brown adipose tissue (BAT)

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Background

Worldwide, breast cancer (BC) is the most commonly diagnosed cancer among women, (excluding non-melanoma skin cancer) [1], and is the second leading cause of cancer-related death in women after lung cancer [2].

So, understanding the biological mechanisms that could affect the progression of this disease could yield new targets for prevention and treatment of advanced stages of BC with subsequently improved survival [3].

^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) is a non-invasive imaging modality used for staging and surveillance of various types of malignancies including BC through imaging of glucose metabolism in cancer cells [4]. Yet, ^{18}F-FDG uptake is not tumor-specific; and several studies have reported a particular pattern of the neck and supraclavicular ^{18}F-FDG uptake without any associated radiologically or clinically detectable pathology [5–7]. Brown adipose tissue (BAT) has been demonstrated to account for this pattern of uptake [8].

BAT is a thermoregulatory organ that consumes stored energy to produce heat through the expression of uncoupling protein 1(UCP1), a process called non-shivering thermogenesis and plays a role in glucose and lipid metabolism [9]. It is particularly abundant in newborns to maintain normal body temperatures. Although the prevalence of BAT declines with age, islets of brown adipocytes remain in the white adipose tissue of adult humans [10]. It is activated by cold exposure, with a higher prevalence in young, women, and lean subjects [11].

A few human ^{18}F-FDG-PET/CT published studies suggested that BAT may play an important role in the development and progression of cancer [3, 4, 9, 10, 12]. However, their results are somewhat conflicting, while some of them suggested that BAT activity is greater in patients with active cancer [3, 9, 10], and higher BAT volume was associated with an increased risk of tumor recurrence/tumor-associated mortality independent of other risk factors, such as gender, age, body mass index (BMI), or tumor type [13]. The other reported a better prognosis of cancer patients with activated BAT [4, 12].

Two recent studies claimed that BAT activation may be a good prognostic factor in BC, one found a positive correlation between BAT ^{18}F-FDG uptake with both human epidermal growth factor receptor 2 (HER2) and progesterone receptor (PR) expression and a negative one with estrogen receptor (ER) expression [4]; and the other found a higher prevalence of activated BAT in luminal B molecular subtype [12].

The aim of the present study was to evaluate the association between the level of BAT metabolic activity detected by PET/CT and clinicopathological characteristics of a tumor in patients with primary BC.

Methods

Study population

This retrospective study was approved by the local Institutional Committee of Medical Ethics with a waiver of consent.

Among all patients with newly diagnosed BC studied with ^{18}F-FDG PET/CT at our institution between January 2017 and May 2020, female patients older than 18 years with available histological data were retrospectively selected. The study comprised 157 consecutive patients with histologically proven breast carcinoma (mean age 50.3 ±12.6 years, range 19–88).

Patient preparation and ^{18}F-FDG PET/CT protocol

All patients underwent ^{18}F-FDG PET/CT imaging after fasting for at least 4–6 h and had blood glucose <180 mg/dl immediately prior to IV administration of approximately 5.18 MBq/kg (0.14 mCi/kg) of ^{18}F-FDG, with a maximum dose of 444 MBq (12 mCi) of ^{18}F-FDG. During the subsequent 60 min following injection (uptake phase), patients were advised to remain seated or recumbent calmly in a comfortable quiet room, covered with a blanket to avoid uptake of the radiotracer at physiological sites as brown fat, which can result in image artifacts. Oral hydration with approximately 1000 ml of water and intravenous injection of furosemide 20 mg was performed after ^{18}F-FDG administration. Patients were asked to empty their bladder immediately before the scan.

During image acquisition, patients were instructed to avoid motion and were allowed to breathe normally without specific instructions.

^{18}F-FDG PET/CT image acquisition and reconstruction

Imaging was performed 60 min after ^{18}F-FDG injection, using a high-spatial-resolution, full-ring PET scanner (Biograph mCT Flow, Siemens Healthcare, Erlangen, Germany), combining Lutetium oxyorthosilicate (LSO)-based PET crystals, and 20-slice CT components. An imaging field of view from the base of the skull to mid-thighs with the arms above the head whenever possible was used; otherwise, the arms were positioned beside the body.

The CT scan was performed before the emission acquisition as a single sweep. Here, slice thickness was 3 mm with a pitch of 0.9 and a tube voltage of 120 kV. The tube current automatically modulated according to the patient's body mass index; a 50–100 mAs was used to achieve good image quality. CT data were used for image fusion and the generation of the CT transmission map. No intravenous contrast was used. PET emission data were acquired in a three-dimensional mode, using continuous table motion (CTM) acquisition mode with an average table speed of 0.9 mm/s.

The imaging data were reconstructed using a point spread function and a time-of-flight algorithm (TrueX + time-of-flight, UltraHD-PET), with 2 iterations and 21 subsets. Subsequently, a Gaussian filter with 5-mm full-width half-maximum was applied to the reconstructed images. For attenuation and scatter correction as well as anatomical mapping, a low-dose CT without contrast agent was used. Transaxial, sagittal, and coronal images as well as fused images were analyzed on manufacturer's workstation (Syngo.via, Siemens Healthcare).

^{18}F-FDG PET/CT image analysis, activated BAT identification, and semi-quantitative evaluation

Retrospective visual and semi-quantitative ^{18}F-FDG PET/CT image analyses were performed in consensus by two experienced nuclear medicine physicians. ^{18}F-FDG uptake in BAT was considered positive when the neck and/or supraclavicular and/or mediastinal and/or paravertebral foci with an uncommonly high ^{18}F-FDG uptake were observed, which corresponding to adipose tissue attenuation on CT images (CT density – 250/–50 Hounsfield units). For each area showing active ^{18}F-FDG BAT uptake, the body weight-normalized maximum standardized uptake value (SUVmax) was calculated by creating a 3-dimensional volume of interest (VOI) assigned to the area of the active focus manually on fused PET/CT images, using PET Volume Computerized-Assisted Reporting on Syngo.via workstation (Siemens Healthcare). In addition, the volume of activated BAT for each region was computed and the total metabolic activity (TMA) was recorded.

The distribution of activated BAT, age, BMI, fasting blood sugar, and gender of patients with activated BAT were recorded.

Axillary lymph nodes showing ^{18}F-FDG uptake greater than the mediastinal blood pool were considered positive for metastasis on PET/CT and confirmed by biopsy or dissection. Distant metastasis was considered if there is any focal abnormal increased ^{18}F-FDG uptake in any part of the scanned skeleton not explained by clinical relevant alternative and or with characteristic CT findings and confirmed by biopsy, another modality (CT or MRI) or follow-up study.

The patient population was divided into two groups according to their age at the time of diagnosis: <50 years and ≥50 years and into two groups according to BMI: BMI <25 and ≥25. The Ki-67 index was categorized as < 14% and ≥14%, and subsequently, primary tumors were classified as luminal A, luminal B, HER2 overexpression (HER2+), and triple-negative (TN) subtypes.

Statistical analysis

Data were analyzed using SPSS 20.0 software (Statistical Package for the Social Sciences, IBM Inc., Armonk, NY).

Continuous parametric variables were expressed as the mean ± standard deviation (SD). Non-parametric variables were displayed as the median and interquartile range (IQR). Categorical data are reported as percentages. Comparisons between continuous variables were performed with an independent sample t test or one-way ANOVA; Mann-Whitney U test was used to compare the medians. Statistical analysis of the categorical variables was conducted using a chi-square test. Person correlation analysis was used to assess the correlation between highest BAT SUVmax as well as TMA; and age, hormone receptor status, level of Ki-67 expression, BMI, outdoor temperature, primary tumor size, and primary SUV max; where the degree of correlation was considered as low (0–0.25), moderate (0.5–0.75), or high (0.75–1). Univariate and multivariate regression analysis was performed to identify the most powerful PET metabolic parameters to predict BAT activation. A P value < 0.05 was considered as statistically significant in all instances.

Results

A total of 157 consecutive female patients with invasive BC were enrolled in this retrospective study, mean age was 50.3 ± 12.6 years (range: 19–88). The clincopathological features of the study population are illustrated in Table 1.

BAT was activated in 16 of the 157 patients (10.2 %), with the majority of patients (15/16) had bilateral ^{18}F-FDG uptake in the supraclavicular regions (Figs. 1, 2, 3, and 4). Three patients had uptake in four regions (two patients had BAT ^{18}F-FDG uptake in cervical, supraclavicular, mediastinal, and paravertebral regions; and one patient had BAT ^{18}F-FDG uptake in cervical, supraclavicular, paravertebral, and perinephric regions). Seven patients had uptake in three regions (four patients had BAT ^{18}F-FDG uptake in cervical, supraclavicular, and paravertebral regions; and three patients had BAT ^{18}F-FDG uptake in cervical, supraclavicular, and mediastinal regions). Three patients had uptake in two regions (two patients had BAT uptake in supraclavicular and mediastinal regions, and one patient had BAT ^{18}F-FDG uptake in supraclavicular and paravertebral regions), and three patients had uptake in one region (two patients had BAT ^{18}F-FDG uptake in supraclavicular region and one patient had BAT ^{18}F-FDG uptake in paravertebral region).

The mean value of highest BAT SUVmax was 13.3 ± 9.9, and the mean value of BAT TMA was 79.6 ± 45 (Table 2).

Median outdoor temperature was significantly lower in the activated BAT group; 26 versus 34 (*P* value=0.035). Patients with BAT activation tended to have a lower median primary tumor size and primary SUVmax, but not

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Table 1 Patients and tumor characteristic according to BAT status

| Parameter	BAT ^{18}F-FDG uptake		P value
	Positive (*n*=16)	Negative (*n*=141)	
Outdoor temperature:			
• Median (IQR)	26 (12)	34 (15)	0.035[b]
Age:			
• <50 years	14 (87.5%)	64 (45.4%)	0.001[a]
• ≥50 years	2 (12.5%)	77 (54.6%)	
BMI:			0.001[a]
• < 25	10 (62.5%)	32 (22.7%)	
• ≥ 25	6 (37.5%)	109 (77.3%)	
Tumor size in cm			0.680[b]
• Median (IQR)	2.5 (0.9)	2.7 (1.8)	
Primary SUVmax			0.979[b]
• Median (IQR)	5.92 (11.96)	8.2 (9.21)	
ER status:			0.668[a]
• Positive	11 (68.6%)	104 (73.8%)	
• Negative	5 (31.2%)	37 (26.2%)	
PR status:			0.783[a]
• Positive	10 (62.5%)	93 (66%)	
• Negative	6 (37.5%)	48 (34%)	
HER2neu:			0.356[a]
• Positive	5 (31.2%)	61 (43.3%)	
• Negative	11 (68.8%)	80 (56.7%)	
Histology :			0.937[a]
• IDC	14 (87.5%)	124 (87.9%)	
• ILC	2 (12.5%)	16 (11.3%)	
• Others	0	1 (0.7%)	
Grade:			0.946[a]
• I	2 (12.5%)	14 (9.9%)	
• II	9 (56.2%)	83 (58.9%)	
• III	5 (31.2%)	44 (31.2%)	
Molecular subtype:			0.801[a]
• Luminal A	5 (31.2%)	35 (24.8%)	
• Luminal B	7 (43.8%)	80 (56.7%)	
• Triple negative	3 (18.8%)	20 (14.2%)	
• HER2+	1 (6.2%)	6 (4.3%)	
Ki-67:			0.507[a]
• <14%	1 (6.2%)	14 (9.9%)	
• ≥14%	8 (50%)	85 (60.3%)	
• Not assessed	7 (43.8%)	42 (29.8%)	
N-stage:			0.823[a]
• N0	5 (31.2%)	48 (34%)	
• N1-3	11 (68.8%)	93 (66%)	
M-stage:			0.862[a]
• M0	13 (81.2%)	117 (83%)	
• M1	3 (18.8%)	24 (17%)	

[a]Chi-square test, [b]Mann-Whitney *U* test
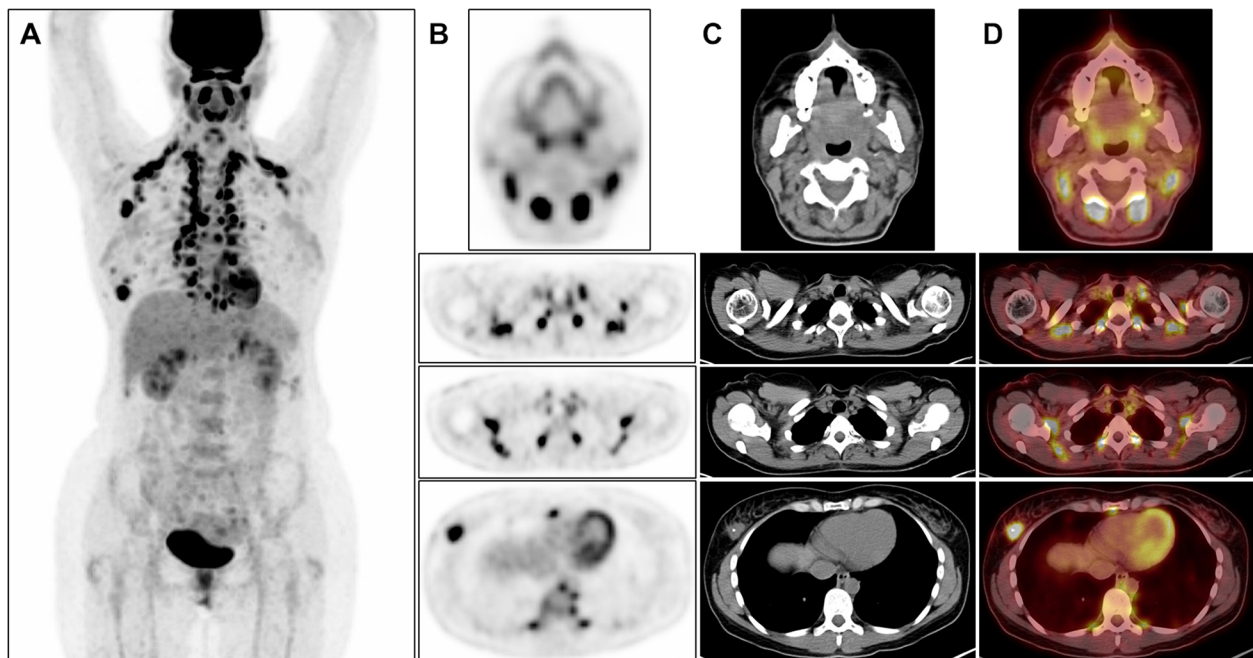
Fig. 1 Brown fat uptake: ^{18}F-FDG PET/CT scan of a 45-year-old female with luminal A invasive ductal carcinoma of the right breast: **a** maximum intensity projection, **b** transaxial PET show intense ^{18}F-FDG uptake in the cervical, supraclavicular, paravertebral, and mediastinal regions. **c** The corresponding CT and **d** transaxial PET/CT fusion images reveal that ^{18}F-FDG uptake is corresponding to fatty tissue, and there is no abnormal lymph node or muscle uptake, denoting activated BAT. The last row show intense FDG-avid primary lesion at the lower outer quadrant of the right breast with a metallic clip in situ, as well as foci of activated BAT at paravertebral, and mediastinal regions
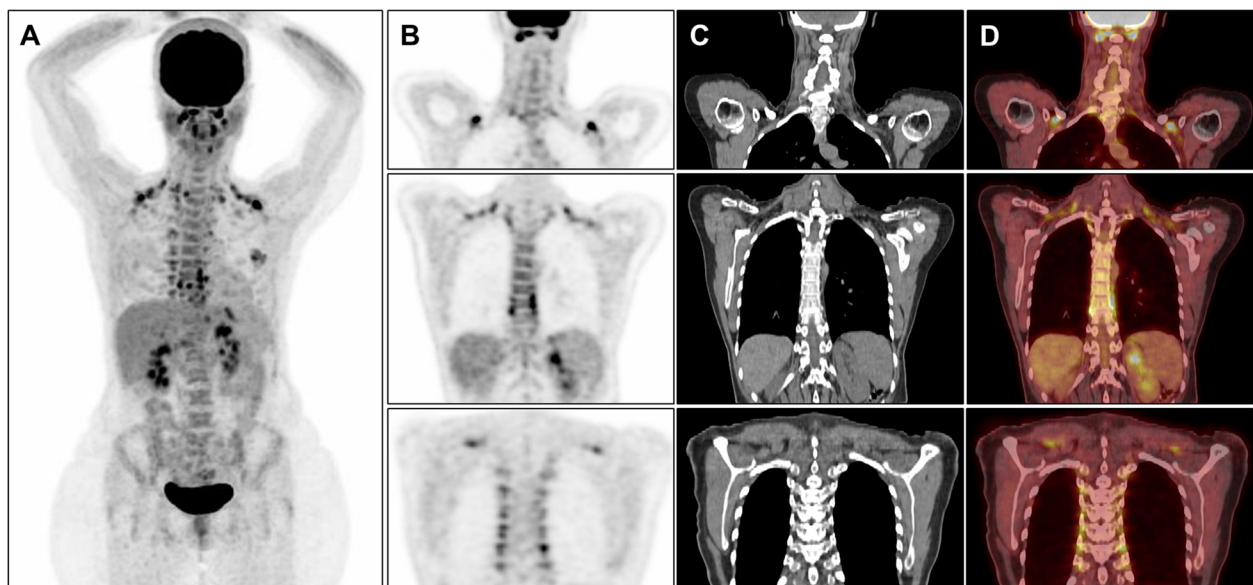

Fig. 2 Brown fat uptake: ^{18}F-FDG PET/CT scan of a 46-year-old female with luminal B invasive lobular carcinoma of the left breast: **a** maximum intensity projection and **b** coronal PET show intense ^{18}F-FDG uptake in the cervical, supraclavicular, and paravertebral regions. **c** The corresponding CT and **d** coronal PET/CT fusion images reveal that ^{18}F-FDG uptake is corresponding to fatty tissue and there is no abnormal lymph node or muscle uptake, denoting activated BAT

Fig. 3 Brown fat uptake: ^{18}F-FDG PET/CT scan of a 41-year-old female with HER2 overexpression left breast cancer: **a** maximum intensity projection and **b** coronal PET show intense ^{18}F-FDG uptake in the cervical, supraclavicular, paravertebral, and perinephric regions. **c** The corresponding CT and **d** coronal PET/CT fusion images reveal that ^{18}F-FDG uptake is corresponding to the fatty tissue and there is no abnormal lymph node or muscle uptake, denoting activated BAT

statistically significant than those without BAT activation.

BAT activation was significantly more frequent among younger age groups (14/16) and patients with lower BMI (10/16), but it was insignificantly more frequent among ER+, PR+, HER2−, invasive ductal carcinoma (IDC), grade II, luminal B subtype, high Ki-67 expression level, patients with positive nodal metastasis, and in patients without distant metastasis (M0) as illustrated in Table 1.

Mean SUVmax was insignificantly higher in younger age group, stages III and IV, invasive lobular carcinoma (ILC), grade I, luminal A subtype, ER+, PR+, Her2−, patients with positive nodal metastasis, and patients without distant metastasis (M0).

TMA was significantly higher among HER2 positive patients (*P* value=0.019), but insignificantly higher among the younger age groups, stages I and II, ILC, grade I, luminal B subtype, ER+, PR−, higher Ki-67
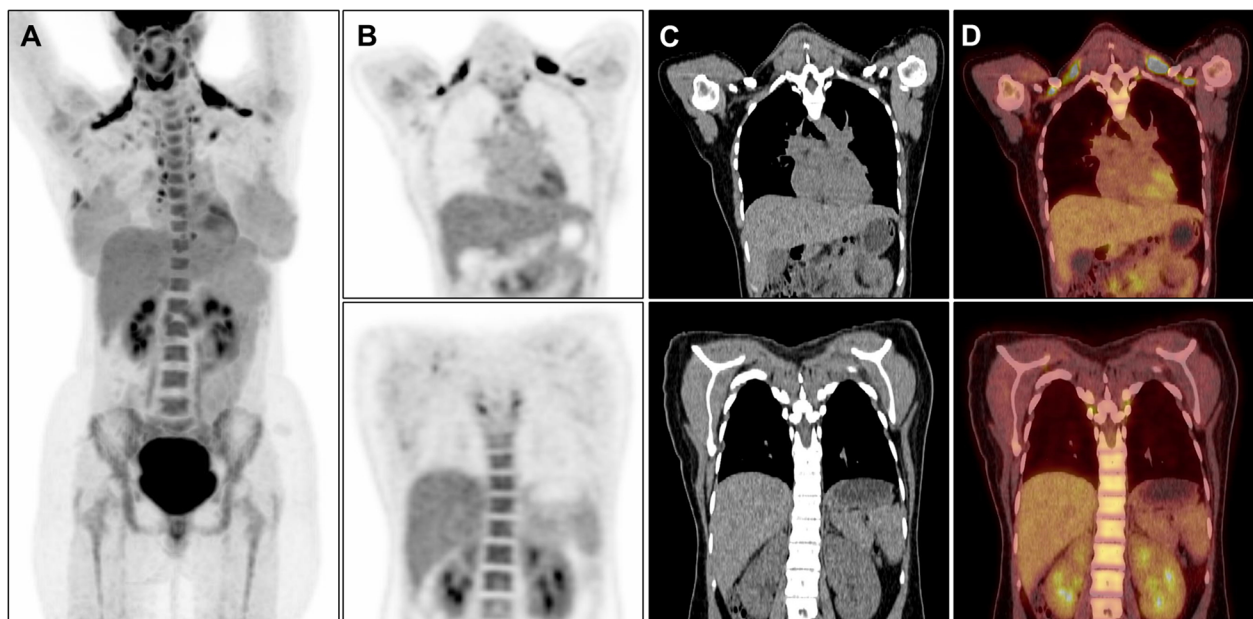

Fig. 4 Brown fat uptake: ^{18}F-FDG PET/CT scan of a 28-year-old female with basal-like right breast cancer: **a** maximum intensity projection and **b** coronal PET show intense ^{18}F-FDG uptake in the cervical, supraclavicular, and paravertebral regions. **c** The corresponding CT and **d** coronal PET/CT fusion images reveal that ^{18}F-FDG uptake is corresponding to fatty tissue and there is no abnormal lymph node or muscle uptake, denoting activated BAT

Table 2 Imaging characteristics of activated BAT on ^{18}F-FDG PET/CT and environmental factors

Parameter	Mean ± SD	Median (range)
BAT (HU)	− 141 ± 20	− 117.5 (− 163 to − 95)
BAT highest SUVmax	13.3 ± 9.9	9.5 (2–33)
BAT TMA	79.6 ± 45	70 (6–195)
Indoor temperature (c)	18.9 ± 0.8	19 (18–20)
Outdoor temperature (c)	32.6 ± 8.3	33 (17–48)

SUVmax maximum standardized uptake value, *TMA* total metabolic activity

expression level, patients with positive nodal metastasis, and patients with distant metastasis (M1) (Table 3).

The highest SUVmax was insignificantly negatively correlated with the age of patients in years, Ki-67 level, BMI, and tumor size ($r=-$ 0.228, – 0.071, and – 0.175 with P value=0.396, 0.480, 0.517, and 0.738, respectively), while TMA was insignificantly positively correlated with Ki-67 and BMI ($r=$0.399 and 0.255 with P value = 0.287 and 0.36, respectively). Both highest SUVmax and TMA were insignificantly positively correlated with SUVmax of the primary tumor (Table 4).

Uni- and multivariate analyses

In univariate analysis, the patient's age, weight in kilograms, BMI, and outdoor temperature were significantly associated with BAT activation. Before the multivariate regression, we performed a collinearity diagnostics of the aforementioned independent variables. We found that there was strong collinearity between the patient's weight and BMI. Eventually, we included patient age, BMI, and outdoor temperature in the multivariate regression analysis. The result demonstrated that BMI (odds ratio [OR] = 3.779, P = 0.025), and patient's age (OR=0.195, P=0.043) were the significant independent predictor factors for BAT activation in BC (Table 5).

Discussion

Metabolically active BAT has been recognized in adult humans after the advent of PET/CT [11, 14, 15]. Different studies have confirmed that adipose tissue does not only store energy but also secretes adipokines, inflammatory cytokines, growth factors, and free fatty acids, which can contribute to tumor growth and cancer progression [16–18]. Moreover, BAT has a similar biological property of hypermetabolism to cancer cells, this allowed in vivo quantification of BAT metabolism, which provided a major advancement in the field of BAT biology [19]. On ^{18}F-FDG PET/CT imaging, BAT is most often detected in the cervical, supraclavicular, mediastinal, and paravertebral regions, and less frequently in the sub-phrenic areas [12]. In accordance, we found among patients with positive BAT, 15/16 (93.75%) patients had active BAT in the cervical,

Table 3 SUVmax and TMA of activated BAT according to patients and tumor characteristics

Parameter	BAT SUVmax		BAT TMA	
	Mean ±SD	P value	Mean ± SD	P value
Age:				0.597[a]
< 50 years	13.7 ±10	0.683[a]	81.9 ± 47.8	
≥ 50 years	10.5 ±10.6		63 ± 15.5	
Disease stage:				0.883[a]
I & II	10 ±9.9	0.148[a]	81 .1 ± 54	
III & IV	17 ±8.8		77.5 ± 34.6	
Histology:				0.256[b]
IDC	13.2 ±10.4	0.978[b]	74.5 ± 33.8	
ILC	13.5 ± 7.7		114.5 ± 13.8	
Grade				0.521[b]
I	18.5±20.5	0.756[b]	92 ± 14	
II	12.4± 8.5		87.8 ± 51.6	
III	12.8 ± 10		59.6 ± 39.2	
Molecular subtypes				=0.272[b]
Luminal A	17±13.4	0.272[b]	72.4 ± 21.2	
Luminal B	10 ±5.7		92.5 ± 55.5	
Basal-like	9.3 ±8.7		43.3 ± 32.5	
HER2+ve	28 ± 0		133 ± 0	
ER receptor status				0.831[a]
Positive	13.5 ± 10	0.936[a]	81.3 ± 45	
Negative	13 ±10		75.8 ± 50.4	
PR receptor status				0.951[a]
Positive	14.5±10	0.554[a]	79 ± 47	
Negative	11.3 ± 10		80 ± 46.5	
Her2-receptor status				0.019[a]
Positive	11.6 ± 10	0.657[a]	117.2± 56.4	
Negative	14 ± 10.4		62.5 ± 27.5	
Ki-level				0.552[b]
<14	33 ± 0	0.112[b]	102 ± 0	
≥14	11.4 ± 6		89.3 ± 52.2	
Not assessed	12.7± 11		65.3 ± 38.4	
N-stage:				0.626[a]
N0	13 ± 12.9	0.936[a]	71 ± 25.1	
N1-3 (mean)	13.5 ±12		83.5 ± 52.5	
M-stage				0.868[a]
M0	24.6 ± 4.9	0.021[a]	78.6 ± 47.3	
M1	10.6 ± 8.8		83.7 ± 43.3	

[a]Independent sample *T* test, [b]One-way ANOVA
SUVmax maximum standardized uptake value, *TMA* total metabolic activity

supraclavicular, mediastinal, and thoracic paravertebral regions, and only one (6.25%) patient had active perinephric BAT (sub-phrenic) as well.

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Table 4 Correlation between highest SUVmax and TMA of activated BAT, and patient's age, level of Ki-67 expression, BMI, outdoor temperature, tumor size, and primary SUVmax

Parameter	Highest BAT SUVmax		BAT TMA	
	r^a	P value	r^a	P value
Age/years	− 0.228	0.396	− 0.002	0.994
Level of Ki-67 expression	− 0.271	0.480	0.399	0.287
BMI	− 0.175	0.517	0.255	0.36
Outdoor temperature	0.021	0.937	− 0.036	0.894
Tumor size in cm	− 0.103	0738	− 0.078	0.8
Primary SUVmax	0.226	0.529	0.289	0.418

[a]Person correlation coefficient
SUVmax maximum standardized uptake value, *TMA* total metabolic activity

Consistent with previous studies [10, 12], the current study showed that BAT activation is significantly associated with younger age, lower BMI, and lower outdoor temperature (P=0.001, 0.001, and 0.035), respectively. On the other hand, other studies found no significant difference between the BMI of patients with metabolically active BAT and that of patients without BAT [5, 8, 20]. Also, in a study done by Fujii et al. [4], discussing the association between BAT and BC, they reported no statistically significant association between the intensity of supraclavicular BAT activity and age or BMI of the patients (P=0.910 and 0.146), respectively.

The incidence of hypermetabolic BAT identified by ^{18}F-FDG PET/CT has been reported in 1.7–9.3% of patients [21]. However, a relatively higher prevalence of activated BAT was found in patients with lymphoma (17%) and BC (15.2–80%) [3, 6, 10, 12, 22]. Our study demonstrated a lower prevalence (10.2%) of active BAT in the included BC patients, this difference could be explained by patients mismatching for age and weight (active versus non-active BAT groups). While in the other studies, analysis of BAT activity was based on age and body weight-matched groups of patients [3, 4, 12].

Given the retrospective nature of our study, we could not obtain the information about the menopausal status for each patient, to overcome this challenge, we stratified the data by age (<50 and ≥ 50 years old) to roughly classify the patients into premenopausal and postmenopausal groups, respectively.

Considering the positive BAT group, we found that active BAT is significantly prevalent in patients <50 years (14/16, 87.5%) versus (2/16, 12.5%) in patients ≥ 50 years, (P=0.001). In addition, the multivariate analysis revealed that BMI and age of the patients were the only factors significantly associated with BAT activity (P= 0.025 and 0.043, respectively). Furthermore, we found a more frequent expression of PR and ER in patients with active BAT, in consistent with other studies which documented higher prevalence of hypermetabolic BAT in non-menopausal patients and suggested that BAT metabolism is sex hormone-dependent and female sex hormones promote ^{18}F-FDG uptake in BAT [6, 23, 24].

Our patients with active BAT showed insignificantly higher prevalence of lymph node metastasis and a lower prevalence of distant metastasis compared to patients without BAT activation. Also, TMA and SUVmax of BAT were insignificantly higher in patients with nodal metastasis. However, we demonstrated a significant positive association between SUVmax of BAT and absence of distant metastasis (P=0.021), this comes in contrast to Pace et al .[12], who documented that patients with active BAT had a significantly less frequent nodal and distant metastasis than in patients without active BAT ($P < 0.05$). Yet, in agreement with our findings, they stated the absence of significant difference in TMA and SUVmax of BAT between patients with and without nodal metastasis.

Moreover, we revealed that active BAT is more frequent in luminal B subtype, HER2−, and grade II, with higher activity of BAT in grade I. Both SUVmax and TMA tended to be higher in less aggressive molecular subtypes (luminal A and B), respectively. Although TMA of BAT was significantly higher among HER2+ patients (P=0.019), in the setting of HER2-targeted therapy, HER2+ BC is no longer associated with poor prognosis [25].

In the present study, we found a negative association between both metabolic activity (SUVmax), size of the primary tumor, and the prevalence of BAT activity, both of them tend to be lower in activated BAT group. Also, there was an insignificant correlation between the

Table 5 Univariate and multivariate logistic regression analysis of the relationship between BAT activation and patient's age, weight, BMI, and outdoor temperature

Variable	Univariate analysis			Multivariate analysis		
	OR	95%CI	P	OR	95%CI	P
Age	0.119	0.026–0.542	0.006	0.195	0.040–0.952	0.043[a]
Weight in kg	1.059	1.012–1.107	0.012			
BMI	0.176	0.059–0.522	0.002	3.779	1.183–12.071	0.025[a]
Outdoor temperature	1.075	1.002–1.154	0.044	1.073	0.996–1.157	0.064

[a]Statistically significant

intensity of metabolic status of the primary tumor and that of BAT. In contrast, other studies found a positive association [4, 9, 10].

Our study had some limitations, the first one being a retrospective analysis, a small number of BAT-positive patients; other factors known to be associated with BAT activation including psychological factors and catecholamine levels and medical history of patients were not evaluated. A large prospective multicenter study is needed to verify the relationship between BAT activation and the long-term outcome of BC patients.

Conclusions

In summary, our findings support that the presence of BAT activation in young age females is sex hormone-dependent, positively associated with less aggressive molecular subtypes of BC, less frequent in patients with distant metastasis. So, we suggest that BAT activation may be a prognostic factor that carries a better prognosis in BC.

Abbreviations
^{18}F-FDG PET/CT: ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography; BAT: Brown adipose tissue; BC: Breast cancer; BMI: Body mass index; ER: Estrogen receptor; HER2: Human epidermal growth factor receptor 2; IDC: Invasive lobular carcinoma; ILC: Invasive ductal carcinoma; IQR: Interquartile range; PR: Progesterone receptor; SD: Standard deviation; SUVmax: Maximum standardized uptake value; TMA: Total metabolic activity; VOI: Volume of interest

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