Factors Affecting Brown Adipose Tissue Activation in Patients with Lymphoma Undergoing 18F-FDG-PET/CT

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Abstract:

Background:18F-FDG PET/CT is an ideal diagnostic tool to investigate the metabolic activation of brown adipose tissue (BAT); high uptake in BAT interferes with scan interpretation.

Aim: To evaluate the factors affecting BAT activation on 18F-FDG-PET/CT in patients with lymphoma.

Methods: 18F-FDG-PET/CT scans of 208 consecutive patients with pathologically proven lymphoma were retrospectively reviewed PET/CT images were analyzed visually for the presence of FDG-avid BAT, its site, and its amount. For each area showing active BAT uptake, the maximum standardized uptake value (SUVmax) was calculated. In addition, the metabolic volume of activated BAT for each region was computed, and then the total metabolic volume (TMV) was recorded.

Results: BAT was activated in 48/208 patients (23.1%), and most of them (45/48) had bilateral uptake in the supraclavicular regions. BAT activation was significantly more frequent among younger age groups ($P \leq 0.01$), female gender ($P = 0.01$), and Hodgkin type (HL) ($P < 0.01$), but it was insignificantly more frequent in patients with higher body mass index (BMI) ($P = 0.07$).

In univariate analysis, the patient's age, sex, pathological type, injected dose, uptake period, fasting blood glucose, and outdoor temperature were significantly associated with BAT activation. Patient's age (OR = 1.124, $P < 0.01$) and outdoor temperature (OR = 1.238, $P < 0.01$) continued to be significant independent predictor factors for BAT activation in multivariate regression analysis.

Conclusion: BAT activation occurs more often in females, younger ages, and patients with HL. Lower outdoor temperature and younger age are the independent variables for prediction of BAT activation.

Keywords: brown adipose tissue,18F-FDG PET/CT, lymphoma

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Background:

Lymphomas are a group of disorders that originate from immune system cells or their precursors. They are known to originate from any organ or tissue in the body [1].

Positron emission tomography/computed tomography (PET/CT) is a very helpful and powerful method for assessing most lymphoma subtypes. This multimodality can properly identify the lymphoma lesion, evaluate the treatment response, and determine the prognosis by registering functional and morphologic data simultaneously [2].

Brown fat, or brown adipose tissue (BAT), participates in non-shivering thermogenesis and generates heat via glucose metabolism [3] and is called as "brown" because of its distinctive brownish macroscopic appearance. Brown adipocytes have a different cellular composition than white adipocytes, which causes this distinct tissue shape [4].

Brown adipocytes produce heat due to the presence of a large number of mitochondria, as well as the high expression of uncoupling protein-1 (UCP1) [5].

In human adults, the common sites of BAT include fat deposits between neck muscles; supraclavicular, axillae, the hilum of the lungs, around the cardiac muscles; peri-renal and adrenal, around blood vessels such as the aorta; and along the vertebral column [6].

18F-FDG-PET/CT is the most utilized imaging method for measuring human BAT activity [7].

Although it is usually easy for nuclear medicine specialists to spot the regions of BAT uptake through its characteristic pattern and from the low attenuation in the CT scan, high activity in BAT can still be mistaken for a malignant lesion or create false-negative results

due to obscuring small metastases and lowering the diagnostic confidence of the scan professional assessment. It interferes with scan interpretation and interferes with scoring [8, 9].

The aim of the study was to evaluate the factors influencing BAT activation on 18F-FDG-PET/CT in patients with lymphoma.

Patients and Methods:

This retrospective study was approved by the local Institutional Committee of Medical Ethics (IRB No. 200041).

The study included adult patients with pathologically proven lymphoma who underwent 18F-FDG PET/CT scanning at the Nuclear Medicine Unit of Assiut University Hospital between July 2019 and July 2022; patients less than 18 years old were excluded. We collected patients' data regarding age, weight, height, previous therapy (chemotherapy or radiotherapy), fasting blood glucose level measured prior to 18F-FDG injection, injected 18F-FDG dose, the time between injection and subsequent imaging (uptake period), and the date of the scan.

- Conditions for adequate patient preparation were sufficiently met to minimize the appearance of potential artefactual uptake patterns that would have made the interpretation inaccurate.
- Patients were routinely instructed to avoid exercise before and on the day of scanning and to fast for at least 4h before imaging.
- Following injection (uptake period approximately 45 to 60 min), patients were kept in totally relaxing, quiet, and warm conditions and advised to avoid excessive talking and maintain adequate hydration (500-1000 ml of plain water).

^{18}F-FDG PET/CT Imaging protocol:

A high-resolution, full-ring PET scanner (Biograph Horizon, Siemens Healthcare, Erlangen, Germany) was used for imaging, which combined lutetium oxyorthosilicate (LSO)-based PET crystals with 16-slice CT components.

A low-dose non-contrast CT scan was obtained by an integrated multi-slice CT machine, an imaging field of view (FOV) from the vertex of the skull to the mid-thighs. Immediately after the low-dose CT, an emission PET scan was obtained in a three-dimensional mode over the same anatomical regions, from the mid-thighs to the vertex of the skull. Transverse image reconstruction was carried out using an iterative technique using reoriented tomograms shown in the transaxial, coronal, and sagittal planes. Axial, sagittal, coronal, and fused images were examined on the manufacturer's workstation (Syngo. via Siemens Healthcare).

Image analysis:

Qualitative assessment:

PET/CT images were analyzed visually, where any lymph node that showed FDG uptake greater than the mediastinal blood pool uptake was considered positive for lymphomatous infiltrate. Extranodal infiltrate was considered positive if there was any focal abnormal increased FDG uptake in visceral, osseous, or marrow regions. On the other hand, the study was defined as negative when there was no evidence of any abnormal FDG uptake all over the scanned body.

18F-FDG BAT uptake was considered positive when there was an uncommonly high uptake in an area corresponding to adipose tissue attenuation on CT images (CT density of −250/−50 Hounsfield units, fat density). BAT uptake was recorded according to its anatomical site (cervical, supraclavicular, mediastinal, axillary, paravertebral, or perinephric regions). The degree of active BAT was determined according to the number of active BAT regions and classified as mild (1 or 2 distribution regions), moderate (3 or 4 regions), and extensive (5 or 6 regions).

Semi-quantitative assessment:

For each area showing active 18F-FDG BAT uptake, the maximum standardized uptake value (SUVmax) was calculated manually by creating a 3-dimensional volume of interest (VOI) assigned to the area of the active focus on the fused PET/CT images on the manufacturer's workstation (Syngo. via Siemens Healthcare). Liver and blood pool SUVmax were calculated by drawing a region of interest over the right lobe of the liver and arch of the aorta, respectively, away from any pathologically high FDG uptake.

In addition, the metabolic volume of activated BAT for each region was measured, and then the total metabolic volume (TMV) was recorded by summation of the volume of all activated regions in the patient.

The patient population was divided into two groups according to their age at the time of diagnosis: a younger age group who were < 50 years and an older age group who were ≥ 50 years; into two groups according to BMI: a lower BMI group < 25 and a higher BMI group ≥ 25; and into two groups according to BAT positive and negative.

The outdoor temperature is obtained from weather data on Google on the date of the PET/CT scan.

The Deauville score is an internationally recommended five-point scale for standard clinical reporting of FDG PET/CT in lymphoma patients. It is based on comparing FDG uptake in the affected regions to that of the mediastinum blood pool and liver.

where score 1 means no uptake, score 2 means uptake ≤ mediastinum, score 3 means uptake > mediastinum ≤ liver, score 4 means moderately increased uptake above that of the liver, and score 5 means markedly increased uptake above that of the liver and/or new sites of disease [10].

Statistical analysis

The researcher checked, coded and analyzed the data using IBM-SPSS 24.0 (IBM-SPSS Inc., Chicago, IL, USA).

Descriptive statistics: continuous data was expressed as means, standard deviations (SD), or medians, range, and interquartile range (IQR), while qualitative data was expressed as frequency and percentages. The chi-

square test was performed to compare the differences in frequency distributions between groups. The Shapiro-Wilk test was used to assess the normality of continuous variables, and accordingly, an independent t-test was calculated to test the differences in the mean between groups, while the Mann-Whitney U test was used for comparison of the differences in the median between groups. Pearson correlation analysis was done to assess the correlation between highest BAT SUVmax as well as TMV and each of age, BMI, injected dose, uptake period, fasting blood glucose, outdoor temperature, liver SUVmax, blood pool SUVmax, and most active SUVmax, where the degree of correlation was categorized as low (0–0.25), moderate (0.5–0.75), or high (0.75–1).

Univariate and multivariate regression analyses were performed to determine the most powerful PET metabolic parameters for predicting BAT activation.

A p-value < 0.05 was considered statistically significant in all instances.

Results:

A total of 208 patients were included in this retrospective study: 105 females (50.5%) and 103 males (49.5%).

The mean age was 42.71 ± 16.31 years (range: 18-81 years), and the median BMI was 28.06 (IQR: 9.58). The mean fasting blood glucose was 110.2±29.15 mg/dl (range: 62-194 mg/dl).

According to pathological type, 89 patients (42.8%) were HL and 119 (57.2%) were NHL. Regarding pathological subtype, most of the patients, 77/208 (37%), were B-cell subtype, 18 patients (8.7%) were nodular sclerosing, while mixed cellularity was found in 12 patients (5.8%).

According to the Deauville score, 22 patients were scored 1, 45 patients were scored 2, 42 patients were scored 3, 44 patients were scored 4, and 51 patients were scored 5. An accurate assessment of the Deauville score could not be reached in four patients due to overlapping BAT activity.

According to the line of treatment, 15 patients did not receive treatment yet (the PET CT scan was ordered for initial staging before therapy), 160 patients received chemotherapy, 30 patients received chemo-radiotherapy, and the remaining 3 patients received radiotherapy (Table 1).

Positive BAT is found in 48 (23.1%) patients of our study population, while the remaining 160 (76.9%) are negative. Fifteen out of 48 patients had extensive BAT distribution (six patients had uptake in the six regions and 9 patients in 5 regions), while 21 patients had moderate BAT distribution (12 patients had uptake in 4 regions and 9 patients in 3 regions), and the last 12 patients showed mild BAT distribution (8 patients had uptake in 2 regions and 4 patients in 1 region), with most of the BAT-positive patients (45/48) having 18F FDG uptake in bilateral supraclavicular regions.

All patients with positive BAT were less than 50 years old (P ≤ .01). The median age of patients with positive BAT was significantly less than those with negative BAT (26 vs. 50 years, respectively, P ≤ .01).

BAT activation was insignificantly more frequent in patients with higher BMI (27 vs. 21, respectively, P value = 0.07).

BAT activation was significantly more frequent among females than males (32 vs. 16 patients, respectively, P= 0.01).

The median outdoor temperature was significantly lower in the activated BAT group: 22 vs. 26, respectively, P ≤ 0.01.

BAT activation was significantly more frequent among HL than NHL (33 vs. 15 patients, respectively, P ≤ 0.01). BAT activation was significantly more frequent among the nodular sclerosing subtype (13 vs. 5 patients, respectively, P ≤ 0.01).

BAT activation was insignificantly associated with the type of treatment received. 33 patients with positive BAT received CTH, 12 patients received chemoradiotherapy, and 3 have not received their treatment yet (P = 0.095) (Table 2).

The median TMV was insignificantly higher in HL than NHL (11.88 vs. 7.88, respectively, P= 0.3). The mean highest SUVmax was insignificantly higher in HL patients (11.8 vs. 9.4, respectively, P=0.2).

The mean TMV was significantly higher among patients with a higher BMI (14.4 vs. 8.7, respectively, P= 0.01). The mean highest SUVmax was insignificantly higher in patients with lower BMI (11.9 vs. 10.4, respectively, p = 0.4).

The median highest SUVmax was significantly higher in female patients than in male patients (10.72 vs. 6.12, respectively, p = 0.034). The median TMV was insignificantly higher among female patients (12 vs. 8.5, respectively, P= 0.86) (Table 3).

In the present study, there was a statistically significant moderate negative correlation between the age of patients and the highest SUVmax of BAT (r = 0.345, p = 0.016). However, there was a statistically insignificant moderate negative correlation between fasting blood glucose and the highest SUVmax (r = -0.280, p = 0.054).

There was a statistically insignificant low negative correlation between BMI, injected dose, outdoor temperature, liver and blood pool SUVmax, and the highest SUVmax (r = -0.112, -0.179, -0.063, -0.023, and -0.010 with p = 0.45, 0.223, 0.670, 0.876, and 0.947, respectively), while uptake period and the most active lymphomatous infiltrate were insignificantly low positively correlated with the highest SUVmax (r = 0.168 and 0.026, p = 0.253 and 0.890, respectively).

The patient's age, uptake period, fasting blood glucose, outdoor temperature, and the most active lymphomatous lesion were insignificantly low negatively correlated with TMV of BAT (r = -0.082, -0.191, -0.197, -0.169, and -0.153, with p = 0.580, 0.194, 0.179, 0.251, and 0.413, respectively), while injected dose, liver, and blood pool SUVmax were insignificantly low positively correlated with TMV of BAT (r = 0.132, 0.140, and 0.244, with p = 0.371, 0.343, and 0.094, respectively).

There was a statistically insignificant moderate positive correlation between BMI and TMV of BAT (r coefficient = 0.304, p = 0.36) (Table 4).

Uni- and multivariate analyses

In univariate analysis, the patient's age, sex, pathological type, injected dose, uptake period, fasting blood glucose, and outdoor temperature were significantly associated with BAT activation. Patient's age (odds ratio [OR] = 1.124, P < 0.01) and outdoor temperature (OR = 1.238, P < 0.01) were the parameters that continued to be significant independent predictor factors for BAT activation in multivariate regression analysis (Table 5).

Table (1): Patients' demographic data and their clinicopathologic characteristics:

Characteristics	Mean ±SD or median	No. (%)
Age in years		
Mean ±SD	42.71±16.31	
Range	(18-81)	
BMI (Kg\m²)		
Median (IQR)	28.06 (9.58)	
Fasting Blood Glucose		
Mean ±SD	110.2±29.15	
Range	(62-194)	
Sex		
Female		105 (50.5%)
Male		103(49.5%)
Pathological types and subtypes		
HL		89(42.8%)
Nodular sclerosing		18(8.7%)
Mixed cellularity		12(5.8%)
Lymphocyte rich		2(1%)
Nodular lymphocyte predominant		2(1%)
Not assessed		55(26.4%)
NHL		119(57.2%)
BCELL		77(37%)
TCELL		3(1.4%)
Follicular		2(1%)
Anaplastic large cell		1(0.5%)
Cutaneous		2(1%)
Marginal zone lymphoma		2(1%)
Burkitt's lymphoma		1(0.5%)
Not assessed		31(14.9%)
Deauville score		
Deauville score 1		22(10.6%)
Deauville score 2		45(21.6%)
Deauville score 3		42(20.2%)
Deauville score 4		44(21.2%)
Deauville score 5		51(24.5%)
Can't be assessed		4(1.9%)
Line of treatment		
No treatment		15(7.2%)
Chemotherapy		160(76.9%)
Chemo-radiotherapy		30(14.4%)
Radiotherapy		3(1.4%)

Table (2): Comparison between positive and negative BAT activity in respect to patient's characteristics and outside temperature.

	BAT		P-value
	Positive (n = 48)	Negative (n = 160)	
Age			
Median (IQR)	26 (16)	50 (26)	≤ 0.01*
< 50	48	79	< 0.01**
≥ 50	0	81	
BMI			
< 25	21	48	= 0.07**
≥ 25	27	112	
Sex			
Males	16	87	= 0.01**
Females	32	73	
Outside Temperature			
Median (IQR)	22 (4)	26 (11)	≤ 0.01*
Pathology type			
HL	33	56	< 0.01**
NHL	15	104	
Pathological Subtypes			
Nodular sclerosing	13	5	
Mixed cellularity	6	6	
BCELL	10	67	
TCELL	2	1	
Follicular	0	2	≤ 0.01*
Anaplastic large cell	0	1	
Cutaneous	0	2	
Marginal zone lymphoma	0	2	
Burkitt's lymphoma	0	1	
Lymphocyte rich	2	0	
Nodular lymphocyte predominant	2	0	
Not assessed	13	73	
Deauville score			
Deauville score 1	7	15	
Deauville score 2	13	32	
Deauville score 3	7	35	=0.003**
Deauville score 4	6	38	
Deauville score 5	11	40	
Can't be assessed	4	0	
Treatment			
No treatment	3	12	
CTH	33	127	= 0.095**
RTH	0	3	
Chemoradiotherapy	12	18	

**Pearson Chi-Square Test

Table (3): TMV and SUVmax of activated BAT according to patient's demographics and pathology type:

Variable	TMV of BAT			Highest SUVmax		
	Median (IQR)	Mean±SD	P value	Median (IQR)	Mean ±SD	P value
Pathology type						
HL	11.48(10.83)		0.322*		11.82±7.08	0.301*
NHL	7.88 (12.40)				9.4±5.2	
BMI						
< 25		8.74	0.015*		11.88±6.76	0.417*
≥ 25		14.38			10.43±6.53	
Sex						
Male	8.54 (15.84)		0.861*	6.12 (7.1)		0.034*
Female	12.00 (9.61)			10.72 (9.31)		
Age						
< 50	11.26 (11.25)		0.002	9.65 (8.85)		0.001

* Mann-Whitney U test

Table (4): Correlation of patient characteristics and TMV, SUVmax of activated BAT

	TMV of BAT		Highest SUVmax	
	Pearson Correlation (r)	P-value	Pearson Correlation (r)	P-value
Age	-0.082	0.580	-0.345	0.016
BMI	0.304	0.36	-0.112	0.45
Injected dose	0.132	0.371	-0.179	0.223
Uptake period	-0.191	0.194	0.168	0.253
Fasting blood glucose	-0.197	0.179	-0.280	0.054
Outside Temperature	-0.169	0.251	-0.063	0.670
Liver SUVmax	0.140	0.343	-0.023	0.876
Blood Pool SUVmax	0.244	0.094	-0.010	0.947
Most active SUVMAX	-0.153	0.413	0.026	0.890

Correlation is significant at the 0.05 level.

Table (5): Univariate and multivariate binary logistic regression analysis of the relationship between BAT activation and the demographic data

Variable	Univariate		Multivariable	
	OR (95% CI)	P-value	(OR) (95% CI)	P-value
Age	1.102 (1.067-1.139)	<0.01	1.124 (1.067-1.183)	<0.01
Sex	2.384 (1.212-4.686)	0.012	2.979 (0.909-9.760)	0.071
Pathology type	0.245 (0.123-0.489)	<0.01	0.946 (0.342-2.618)	0.914
Treatment	2.667 (0.619-11.493)	0.188	1.327(0.169-10.406)	0.788
Injected dose	1.252 (1.017-1.542)	0.034	1.506 (0.686-3.304)	0.307
Uptake period	0.985 (0.972-0.997)	0.015	1.002(0.981-1.023)	0.883
Weight	1.013 (0.994-1.031)	0.176	0.894(0.566-1.412)	0.631
Height	0.991 (0.953-1.031)	0.655	1.036 (0.724-1.483)	0.847
Fasting blood glucose	1.029 (1.013-1.046)	<0.01	1.019 (1.000-1.039)	0.054
Outdoor Temperature	1.165 (1.084-1.252)	<0.01	1.238 (1.119-1.368)	<0.01
BMI	1.036 (0.985-1.090)	0.166	1.158 (0.391-3.429)	0.792

OR, odds Ratio; CI, Confidence Interval

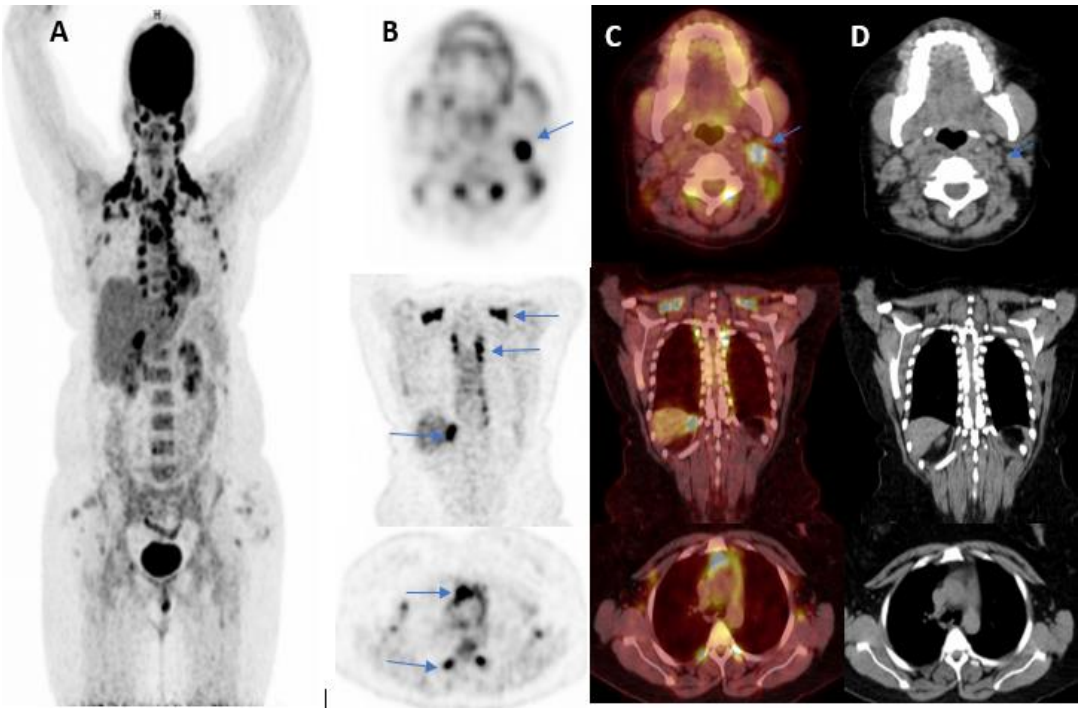

Figure 1: A 40-year-old female diagnosed with non-Hodgkin's lymphoma, B cell subtype, (A) maximum intensity projection image shows extensive brown fat uptake in the six regions (cervical, supraclavicular, mediastinal, axillary, paravertebral, and perinephric regions). (B) coronal and transaxial PET images, (C) coronal and transaxial PET/CT fused images, and (D) the corresponding CT reveal that 18F-FDG uptake corresponds to fatty tissue (HU of -113). The first row shows metabolically active cervical LNs; the accurate judgment of SUVmax and Deauville score cannot be assessed due to overlapping BAT activity.

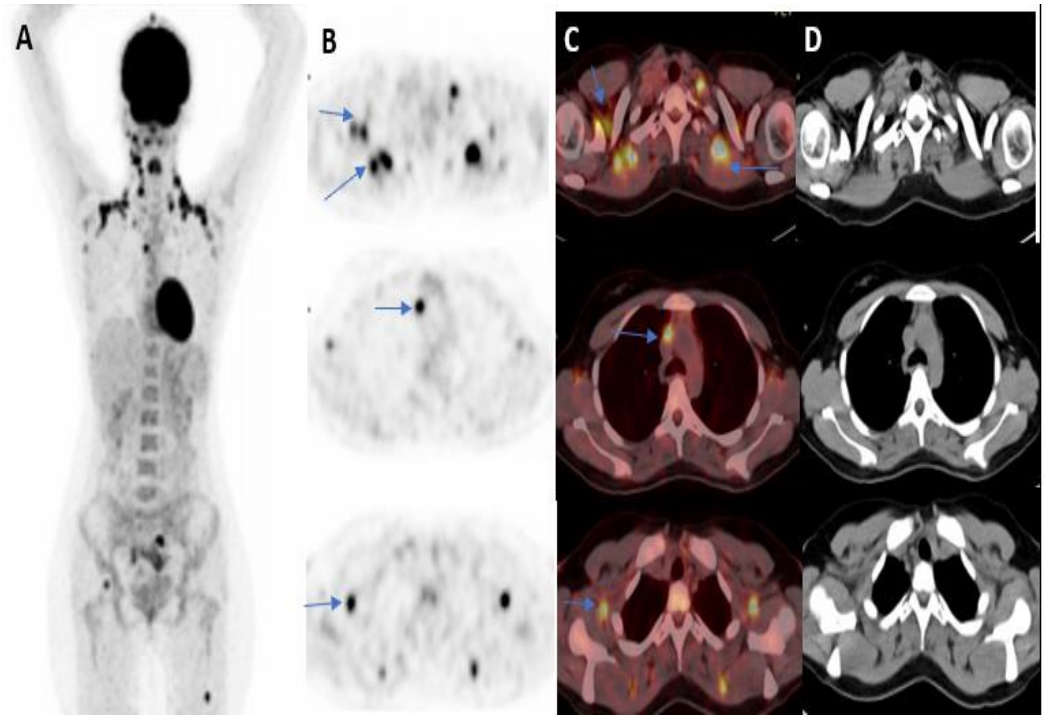

Figure 2: A 20-year-old female diagnosed with Hodgkin lymphoma, nodular lymphocytic predominant subtype (A), maximum intensity projection image shows moderate brown fat uptake in **three** regions (supraclavicular, mediastinal, and axillary regions); (B) transaxial PET images; (C) transaxial PET/CT fusion images. and (D) the corresponding CT reveals that 18F-FDG uptake is corresponding to fatty tissue (HU of -100).

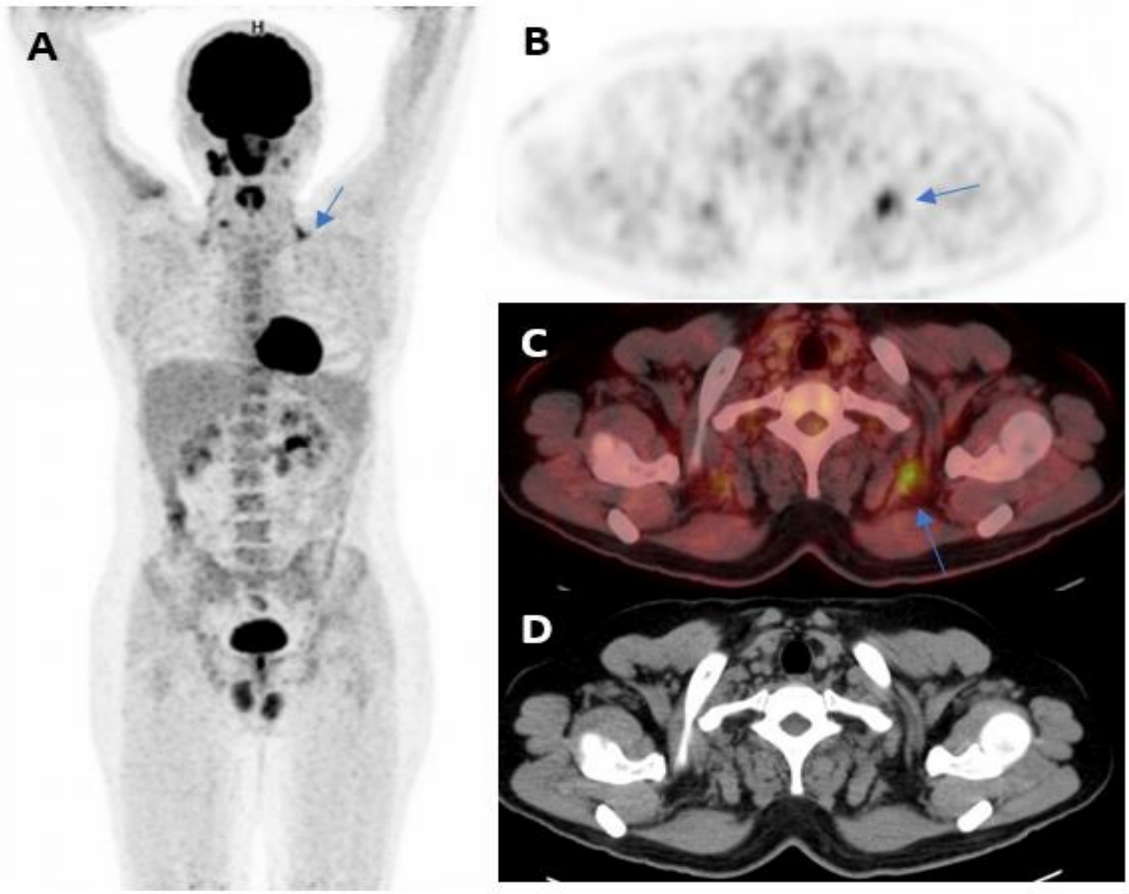

Figure 3: A 30-year-old male diagnosed with Hodgkin lymphoma, mixed cellularity subtype, (A) maximum intensity projection image shows mild brown fat uptake in the supraclavicular region only, (B) transaxial PET images, (C) transaxial PET/CT fused images, and (D) the corresponding CT reveal that 18F-FDG uptake corresponds to fatty tissue (HU of -90).

Discussion:

Metabolically active brown adipose tissue has been identified in adult humans following the introduction of PET/CT imaging [11-13]. Various research studies have established that adipose tissue serves not only as an energy reservoir but also releases, inflammatory cytokines adipokines, free fatty acids, and growth factors, all of which can play a role in the development and progression of tumors and cancer [14-16].

Additionally, because BAT and cancer cells share the biological characteristic of hypermetabolism, it was possible to quantify BAT metabolism in vivo, which significantly advanced the area of BAT biology [17].

The higher glucose uptake within the active BAT allows for its identification in patients using 18F FDG PET/CT; such physiological activity could either mask an underlying disease finding or compromise the correct metabolic assessment of surrounding lesions [18].

BAT is most commonly found on 18F-FDG PET/CT imaging in the cervical, supraclavicular, axillary, mediastinal, paravertebral, and less common peri-nephric regions [19, 20].

According to reports, 1.7–9.3% of patients have hypermetabolic BAT detected by 18F-FDG PET/CT [21]. Patients with lymphoma (17%) and BC (15.2%–80%) had a comparatively greater incidence of activated BAT [19, 20, 22].

In our study we found positive BAT in forty-eight (23.1%) patients, while the remaining 160 (76.9%) were negative. This figure is more than that found by Mostafa et al., who found a prevalence of 10.2% among their studied populations. This may be attributed to our larger sample size (208 compared to 157 patients) [23].

We noticed that most of the patients (93.75%) had 18F FDG uptake in bilateral supraclavicular regions, which is consistent with Farghaly et al. and Mostafa et al., who found values of 95.5% and 93.75%, respectively [23, 24].

Regarding the positive BAT group, BAT activation was significantly more frequent among females than males (32 vs. 16 patients, respectively, P = 0.01). This is similar to Farghaly et al., and in contrast, Pötzsch et al. found that BAT frequency did not differ between females and males (52 vs. 42, respectively, p = 0.563) may be because they studied only younger lymphoma

patients where BAT activity in general more than adults. [24, 25].

In agreement with Huang et al., Cohade et al., Truong et al., Yeung et al., and Farghaly et al., the current study showed that activation of BAT is significantly associated with younger age and lower outdoor temperature ($P < 0.01$ and ≤ 0.01, respectively) [8, 20, 24, 26].

We noticed no significant association between the BMI of patients and BAT activation, in contrast to Mostafa et al. and Steinberg et al., who found a significant association between BAT activation and BMI [23, 26].

We found no significant association between BAT activation and the type of treatment received ($P = 0.095$). This matched with Brendle et al., except for a small group of their patients who received chemotherapy with Adriamycin, bleomycin, vinblastine, and dacarbazine (ABVD) regimen, who were associated with a higher prevalence of BAT activity ($p = 0.01$) [27] .

BAT activation was significantly more frequent among HL than NHL (33 versus 15 patients, respectively, $P \leq 0.01$); additionally, it was significantly more frequent among the nodular sclerosing subtype ($P \leq 0.01$). That was similar to Brendle et al., who found significantly more frequent BAT activation among HL than NHL (36 vs. 19, P value ≤ 0.02), while in contrast to Bakhshayeshkaram et al., who found 27 HD vs. 62 NHL in their study population due to larger number of patients diagnosed as NHL [17, 27].

Brown adipose tissue, one of the main sources of false positive findings on F-18 FDG PET/CT, matched with this fact; we encountered four cases in which the Deauville score could not be accurately assessed due to overlapping BAT activity [28].

The TMV and highest SUVmax were significantly higher in younger patients ($p=0.002$ and 0.001, respectively); the same was concluded by Mostafa et al., but with no statistical significance ($p=0.597$ and 0.683, respectively) [23].

The highest SUVmax was significantly higher in female patients than in males ($P = 0.034$). This is similar to Bakhshayeshkaram et al. and Truong et al. ($P = 0.007$ and $P = 0.012$, respectively) [8, 17].

We found that the TMV was significantly higher among patients with higher BMI ($P=0.01$) and insignificantly higher among female patients, which disagreed with Huang et al., who found no significant association between BMI, sex of patients, and TMV of BAT ($P=0.658$, $P=0.861$, respectively) [20].

Matched with Bakhshayeshkaram et al., we found that the highest SUVmax of BAT was insignificantly higher in HL than NHL ($P= 0.3$) [17].

Regarding the correlation of patient characteristics and the highest SUVmax of activated BAT, we noticed a statistically significant moderate negative correlation between the highest SUVmax and age ($r = -0.345$, $p = 0.016$). This is similar to the results of Bakhshayeshkaram et al. ($r = -0.32$, $p = 0.015$). In contrast, Mostafa et al. found an insignificant low negative correlation between SUVmax and age. ($r = -0.228$, $p = 0.396$) may be due to his smaller sample size [17, 23].

We found statistically insignificant low negative correlation between BMI, outdoor temperature, and highest SUVmax ($r = -0.112$, -0.063, $p = 0.45$, 0.670), matched with those of Mostafa et al. ($r = -0.175$, -0.021, $p = 0.517$, 0.937) [23].

Additionally, the fasting blood glucose level was moderately negatively correlated with the highest SUVmax ($r = -0.280$, $p = 0.054$). The injected dose, liver SUVmax, and blood pool SUVmax were insignificantly low and negatively correlated with the highest BAT SUVmax ($r = -0.179$, -0.023, -0.010 with $p = 0.223$, 0.876, and 0.947, respectively), while the uptake period and the most active lymphomatous infiltrate were insignificantly positively correlated with the highest BAT SUVmax ($r = 0.168$, 0.026, $p = 0.253$, 0.890, respectively).

In our study, age, fasting blood glucose, and outdoor temperature were insignificantly low and negatively correlated with TMV of BAT ($r = -0.082$, -0.197, -0.169, with $p = 0.580$, 0.179, 0.251, respectively), in contrast to Huang et al., who found a statistically insignificant low positive correlation between TMV of BAT, age, fasting blood glucose, and outdoor temperature ($r = 0.084$, 0.112, 0.101, with $p = 0.658$, 0.554, 0.596, respectively)mostly due to our larger number of activated group (48 vs 30) [20].

In agreement with Mostafa et al. and Huang et al., BMI was insignificantly positively correlated with TMV of BAT ($p = 0.36$ vs. $p = 0.36$ and 861, respectively). On the other hand, Bos et al. found a significant positive correlation between TMV and BMI ($p = <0.0001$) mostly because values of BMI of our study are higher due to different country and populations [20, 23, 29].

Additionally, we found that the uptake period, outdoor temperature, and the most active lymphomatous lesion were insignificantly low negatively correlated with TMV of BAT ($r = -0.191$, -0.153 with $p = 0.194$, and 0.413, respectively), while the injected dose and liver and blood pool SUVmax were insignificantly low positively correlated with TMV of BAT ($r = 0.132$, 0.140, and 0.244, with $p = 0.371$, 0.343, and 0.094, respectively).

In univariate analysis, the patient's age, sex, fasting blood glucose, pathology type, and outdoor temperature were significantly associated with BAT activation. Only the patient's age and outdoor temperature continued to be the significant independent predictors for BAT activation in multivariate regression analysis ($P < 0.01$ for both). This matched with Steinberg et al., who concluded that the patient's age, sex, BMI, fasting blood glucose, and outdoor temperature were significantly associated with BAT activation in univariate analysis, while the age, sex, BMI, and outdoor temperature were the significant predictor factors in multivariate regression analysis ($P < 0.01$ for all) [26].

In contrast, Bakhshayeshkaram et al. found no significant association between BAT activation and each of sex, pathological type, and outdoor temperature

in univariate regression, and only the age of patients was significantly associated with BAT activation in univariate analysis and continued to be the significant predictor factor in multivariate regression analysis this may be due to different country, included seasons of the year and larger sample size [17].

Limitations

Our study limitations include being a retrospective study and a small number of BAT-positive individuals; other factors, such as medical history of patients, catecholamine levels, and psychological factors known to be associated with BAT activation, were not evaluated. Also, no interventions to reduce activated BAT, such as a beta-blocker, were used.

Conclusion:

BAT activation occurs more often in females, younger ages, and patients with HL; lower outdoor temperatures are associated with more frequent and more extensive BAT activation. Younger age and lower outdoor temperature were the significant independent predictor factors for BAT activation.

The understanding of the factors that influence BAT activation may help to know interventions to minimize BAT activation and to identify patients with lymphoma at risk of BAT activation during 18F-FDG PET scans for BAT-positive patients for accurate assessment of Deauville score.

Recommendation

- We recommend a future large prospective study including other factors that may affect BAT activation.
- Using preventive measures in patients at risk of BAT activation, such as warming and beta-blockers.

Abbreviations

18F-FDG Fluorine-18-fluorodeoxyglucose
ABVD Adriamycin, bleomycin, vinblastine, and dacarbazine
BAT Brown adipose tissue
BMI Body mass index
CT computed tomography
FOV Field of view
HL Hodgkin type
IQR Interquartile range
LSO Lutetium oxyorthosilicate
PET Positron emission tomography
SD Standard deviations
SPSS Statistical Package for the Social Sciences
SUVmax Standardized uptake value
TMV Total metabolic volume
UCP1 Uncoupling protein-1
VOI Volume of interest

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