**Original Article, PET/CT.**

# Revised Mapping of Brown Fat on $^{18F}$ (FDG) Positron Emission Tomography / Computed Tomography (PET/CT).

**Farghaly H. [1,2] Ashour, N.[1], Alqarni, A.[1], Mohamadien, N.[2], Abdelaal, A. [2], Albatly, A.[1] , Almutairy, S.[1], Almukhailed, O.[1], Nasr,H.[1],[3]**

[1] *Department of Radiology, Prince Sultan Military Medical City, Riyadh, Saudi Arabia*

[2] *Department of Oncology and Nuclear Medicine, Faculty of Medicine, Assiut University, Egypt*

[3] *Department of Oncology and Nuclear Medicine, Faculty of Medicine, Cairo University, Egypt*

**ABSTRACT**:

**Aim:** To create a regional body map for FDG-avid (activated) brown adipose tissue (BAT) and to assess the magnitude of BAT activation concerning the time of the year the study was conducted. **Material and Methods:** PET/CT studies with FDG-avid BAT were included. BAT was classified based on its site as typical (frequent and predominantly superficial) or atypical (infrequent and predominantly deep). A score was generated for the overall brown fat (BFS-O), typical brown fat (BFS-T), and atypical brown fat (BFS-A) by summation of activated sites in each scan. The presence of brown fat was examined against time of the year the scan was conducted. The year was divided into two seasons (cold/hot), based on the average temperature in Riyadh, Saudi Arabia. **Results:** We included 291 studies for 215 patients (mean age 27.6 ± 13.0 years; 56.9% females). Active BAT was found predominantly in supraclavicular, cervical, axillary, and paravertebral areas. These locations were considered typical sites and all patients had at least one of them involved. Atypical BAT sites were deeper in location and less frequently activated (50.5%). BFS-O and BFS-A were higher in the cold season. BFS-O >4 was the best cutoff for identifying studies performed during the cold season (p=0.004). More BFS-O of >4 and more frequent atypical BAT sites were detected during the cold season. BFS-T and BFS-A were found to be positively correlated (rho=0.369; p<0.001). Age was negatively correlated with BFS-O, BFS-T, and BFS-A (rho=-0.184; p=0.002), (rho=-0.195; p<0.001), and (rho=-0.116; p=0.049) respectively. Patients with BFS-O of >4 or those with atypical BAT sites were younger.

**Conclusion:** When present, active BAT is virtually always observed at one or more typical sites, but atypical sites are detected in a patient's subset with more extensive BAT activation. Atypical BAT activation was more frequent in younger patients and during colder months of the year.

**Corresponding author:** Hatem Nasr. **E-mail:** hatemnasr@gmail.com

**Submission date 1-3-2024** **Acceptance date 30-4-2024**

## INTRODUCTION:

BAT drives a process of non-shivering thermogenesis, inducing energy expenditure to produce heat and preserve body core temperature during cold weather. During this process, the stored energy of mitochondria is utilized for the generation of heat through the activation of uncoupling protein-1 (UCP-1), as opposed to its conversion to adenosine triphosphate (ATP) [1]. It is also significantly implicated in the metabolism of glucose and lipids [2]. It is most evident during the early stages of life, particularly in newborns. However, as individuals age, the prevalence of this type of tissue gradually decreases to form islets, or distinct clusters, of brown adipocytes within the white adipose tissue found in adult humans [3]. Recent advances in functional imaging technology have also confirmed the presence of BAT in adult human subjects[4]. These islets are activated by exposure to cold, with higher prevalence in young persons, women, and more lean subjects[4].

$^{18}$F FDG PET/CT is an ideal imaging technique to investigate the metabolic activation of BAT [5]. In 2002, Hany et al. utilizing $^{18}$F FDG PET/CT initially documented high $^{18}$F FDG activity in adipose tissue reservoirs located in the neck, near large vessels in the thorax, the axillary regions, perinephric regions, intercostal spaces along the spine, and in the para-aortic regions [6, 7]. The enhanced glucose uptake within the active BAT enables its detection in patients on $^{18}$F FDG PET/CT. Such physiological activity may potentially mask an underlying pathological finding or impair the accurate metabolic characterization of nearby lesions [8].

There has been a growing interest in investigating BAT in humans lately [9]. $^{18}$F FDG PET/CT is considered a unique tool to assess the extent and severity of BAT energy expenditure after cold exposure [10]. Exposure to cold has been linked to BAT activation and enhanced BAT FDG uptake [11].

Various factors have been identified to affect BAT activation. These include age, sex, body mass, plasma glucose, seasonal temperature variations, as well as pharmaceutical agents. [7],[12, 13]. Some studies have been concerned with the activation of BAT after cold exposure [14, 15]. Also, BAT has been correlated to some diseases such as obesity, diabetes, cachexia, atherosclerosis, and constitutional leanness [16].

The objective of this study was to pinpoint the potential typical and atypical anatomical sites for BAT activation. Although the typical sites are more widely known, the knowledge of the less frequent atypical sites would be helpful to take in consideration during the interpretation of $^{18}$F FDG PET/CT scans.

## PATIENTS and METHODS:

After receiving approval from our Institutional Review Board, waiving the requirement for informed consent for this retrospective study, we scanned all PET/CT studies spanning from 2011 to 2019 for the presence of FDG BAT

uptake. On our local RIS system, we performed a text search for the terms “brown fat” or “brown adipose tissue” within the reports of all FDG PET/CT studies performed between the beginning of 2011 to the end of 2019 (8454 studies). The search retrieved 338 PET/CT reports containing these terms. The images for these 338 studies were reviewed and only 291 PET/CT studies that were found to have activated BAT were included in our analysis. Patients' demographics, sites of FDG avid BAT, and scan date were among the data collected.

**Image Acquisition and Reconstruction**

Patients were directed to fast for 4 to 6 hours before the study. Blood glucose levels were checked before administration of the radiotracer and were required to be less than 180 mg/dl just before receiving 5.18 MBq/kg of $^{18}$F FDG, with a capped maximum dose of 444 MBq (12 mCi). Whole body F-18F FDG PET/CT imaging was conducted approximately 45–60 minutes following the radiotracer injection, using a Gemini TF PET/CT machine from Philips. Patients were kept in a tranquil environment, draped with a blanket, and instructed to refrain from conversation or muscular activity for about 40-60 minutes following injection and prior to scanning, to minimize the likelihood of increased physiological radiotracer uptake, especially in muscles, that can induce images artifacts, preclude interpretation or induce false-positive readings. Without instructions, patients were permitted to breathe ordinarily during image acquisition. The emission data for 11–14 bed positions were collected. Emission scans were always acquired in a three-dimensional (3D) mode at a rate of 1 minute per bed position, though the time was increased to 2 minutes per bed position for obese patients BMI>35). The field of view (FOV) extended from the top or base of the skull down to the mid-thigh with the arms typically positioned above the head, unless the patient had predominantly a cervical pathology or could not tolerate positioning the arm above the head. The 3D acquisition parameters included a 128 x 128 matrix, 18 cm FOV with 50 percent overlap. The PET/CT scanner's CT scan included 16 individual slices of imaging data. The maximum patient port height for a gantry is 70 cm. Dimensions of computed tomography: Single-scan parameters are 120–140 kV and 50–100 mA (body mass index dependent), 0.5 s per CT rotation, 1.675:1 pitch, 5 mm slice thickness, and a 512 x 512 matrix. The CT scan was taken first, followed by the emission scan. The CT transmission map and image fusion were both made possible with CT data. There was no use of intravenous contrast. One method of breathing involves holding one's breath after normal exhalation. Shallow breathing is permitted if the patient is unable to breathe deeply.

**Data Interpretation**

On PET/CT scans, image analysis was used to find out where and how much FDG was taken up by BAT. The existence of active BAT is determined by visually detecting the combination of two crucial features on the $^{18}$F FDG

PET/CT images: an abnormally high $^{18}$F FDG uptake on PET images, together with an underlying radio-density on the concomitant CT images indicating the existence of adipose tissue (fat density).

Brown fat was further divided into two groups based on where it was found: typical (more frequently activated and more superficial in location) or atypical (less frequently activated and deeper in location). To reflect the extent of BAT activation, a semi-quantitative brown fat score (BFS) was applied for the total brown fat (BFS-O), for the typical brown fat (BFS-T), and for the atypical brown fat (BFS-A) by adding up the number of activated BAT regions involved in each scan. We dealt with repeated studies as separate studies with brown fat scores calculated for each study separately and analyses were made for each study according to the associated variables at the time of the study as the patient's age and time of the study during the year. We assessed the amount of brown fat concerning the time of the year the scan was conducted. The average weather in Riyadh, Saudi Arabia, was used to split the year into two meteorological seasons. A hot season of 7 months (April to October) and a cold season of 5 months (November to March).

**Statistical analysis:**

Using IBM-SPSS 26.0 (IBM-SPSS Inc., Chicago, IL, USA), the data was analyzed. Calculations of means and standard deviations were made. The unpaired student T-test was utilized to compare the means of continuous variables. ROC analysis was used to determine the optimal BFS cutoff values that best identify the subgroups associated with each season of the year. To compare differences in frequency between categorical variables, the Chi-square test was utilized. Spearman correlation was utilized to determine the relationship between different scores or between scores and patients' age. A p-value is regarded as significant when it is less than 0.05.

## RESULTS:

We included 291 studies for 215 patients with a mean age of 28.9±13.64 years (range 3-81 years), of whom 56.9% were females. Forty-seven patients had repeated scans ranging from 2 and up to 4 scans. Regarding patients with repeated scans, the time interval between scans ranged from 57 days to 5.1 years (mean 17.6 ± 16.63 months). Active brown fat was found most often in the supraclavicular, cervical, axillary, and paravertebral areas, where it was found in 95.5%, 79.7%, 72.5%, and 50.95 % of studies, respectively. These locations are relatively more superficial in position, with almost all patients exhibiting involvement at least at one of these typical sites. The other atypical BAT sites were activated less frequently (50.5%) and tend to be more deep. In order of decreasing frequency, these sites are the abdominal paraaortic, mediastinal, peri hepatic, suprarenal, subscapular, para colic, retro crural, perinephric, para-psoas, pericardial, and subpectoral regions **(Table 1)**.

**Table 1.** Active brown fat map in 291 studies.

| Active Brown Fat Site | Number of studies (%) | |
|---|---|---|
| Supraclavicular | 278 (95.5) | **Typical** 290/291 (99.7%) |
| Cervical | 232 (79.7) | |
| Paravertebral | 211 (72.5) | |
| Axillary | 148 (50.9) | |
| Abdominal Paraaortic | 70 (24.1) | **Atypical** 147/291 (50.5%) |
| Mediastinal | 67 (23.0) | |
| Perihepatic/Subdiaphragmatic | 45 (15.8) | |
| Suprarenal | 39 (13.4) | |
| Subscapular | 19 (6.5) | |
| Paracolic | 18 (6.2) | |
| Retro crural | 14 (4.8) | |
| Perinephric | 12 (4.1) | |
| Para-psoas | 5 (1.7) | |
| Pericardial | 1 (0.3) | |
| Subpectoral | 1 (0.3) | |

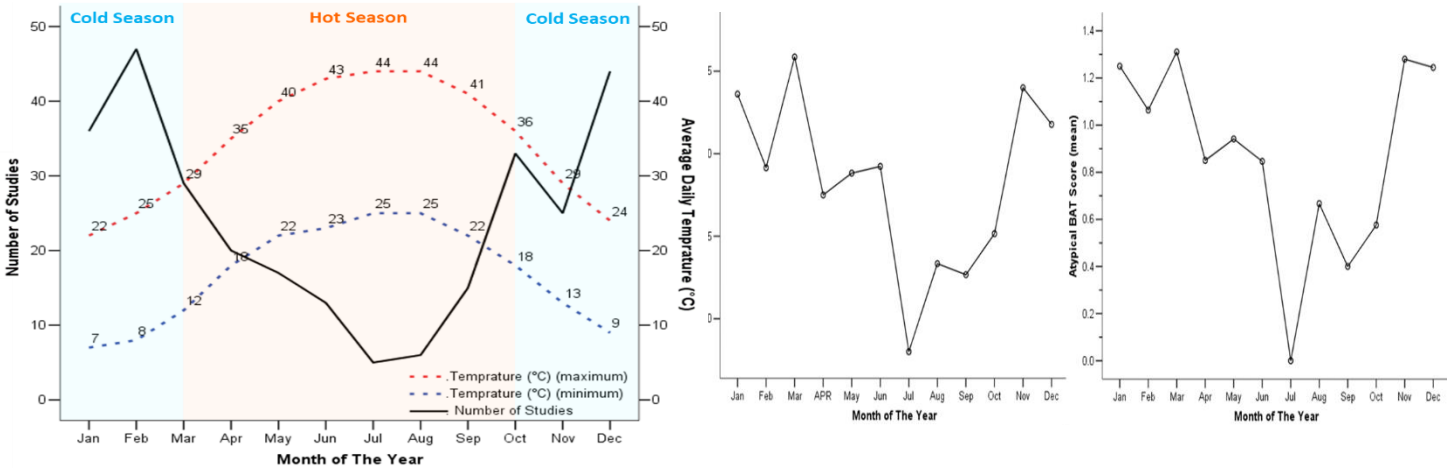


**Figure 1.** The upper panel displays the frequency of studies with activated BAT distributed over the months of the year with a background reflecting hot & cold seasons and associated with plots of average maximum and minimum temperatures during year months in Riyadh city as derived from historical climate archives. The lower panel displayed distribution and changes in the mean overall brown fat score (left) and the mean atypical brown fat score (right) over the months of the year.

There is a significantly more number of studies with activated brown fat during the cold season compared to hot season (182 [62.5%) versus 109 [37.5%]; p<0.001). This is displayed against the months of the year in the upper panel of figure 1 with associated plots of average maximum and minimum temperatures during months of the year in Riyadh city as derived from historical climate

archives [17]. The BFS-O is generally higher in the cold season months compared to the hot season months (**Figure 1**). The mean BFS-O and BFS-A were substantially higher in the cold season than in the hot season of the year (4.24 ± 2.05 compared to 3.59 ± 1.69; p=0.004) and (1.21 ±1.46 compared to 0.67 ± 1.05; p<0.001), respectively. However, the difference in the mean BFS-T between the hot and cold seasons was not statistically significant. No statistically significant differences were found in mean BAT scores between males and females.

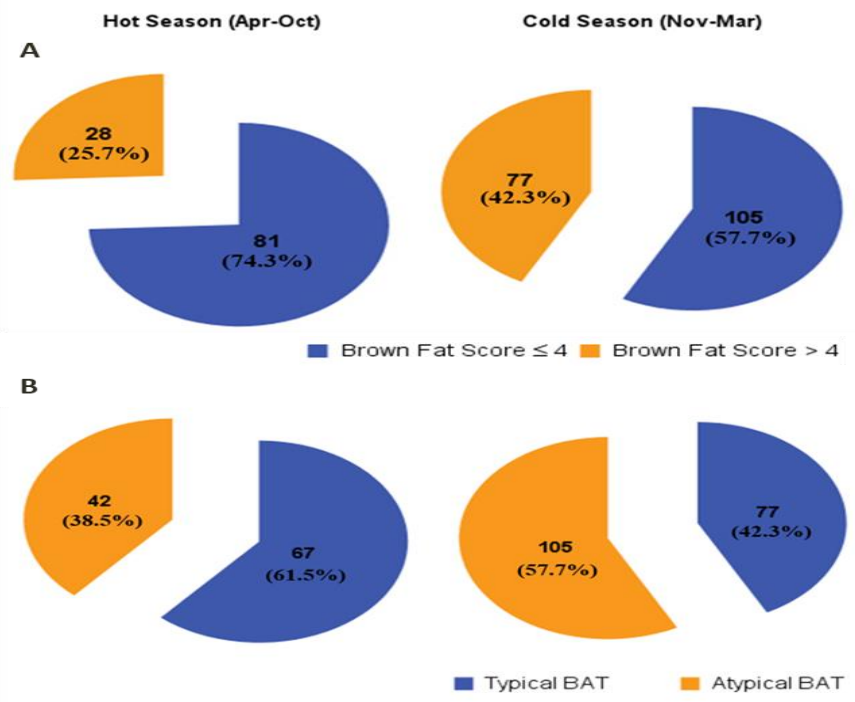


**Figure 2.** A) Frequency of overall brown fat scores (BFS-O) ≤4 and >4 during the hot season and cold season. B) Frequency of typical versus atypical activated brown fat during hot season and cold season months.

Based on ROC analysis (AUC=0.590; p=0.008), a BFS-O cutoff value of >4 was optimal for identifying patient subgroups associated with cold or hot seasons of the year, with sensitivity, specificity, PPV, NPV, and accuracy of 42.3%, 74.3%, 73.3%, 43.5%, and 54.3%, respectively (p=0.004). Studies conducted during the cold season revealed more frequency of BFS-O of >4 (25.7% compared to 42.3%; p=0.004) (**Figure 2A**) and more frequency of atypical brown fat sites (57.7% compared to 38.5%; p=0.002) (**Figure 2B**) than studies conducted during the warm season.

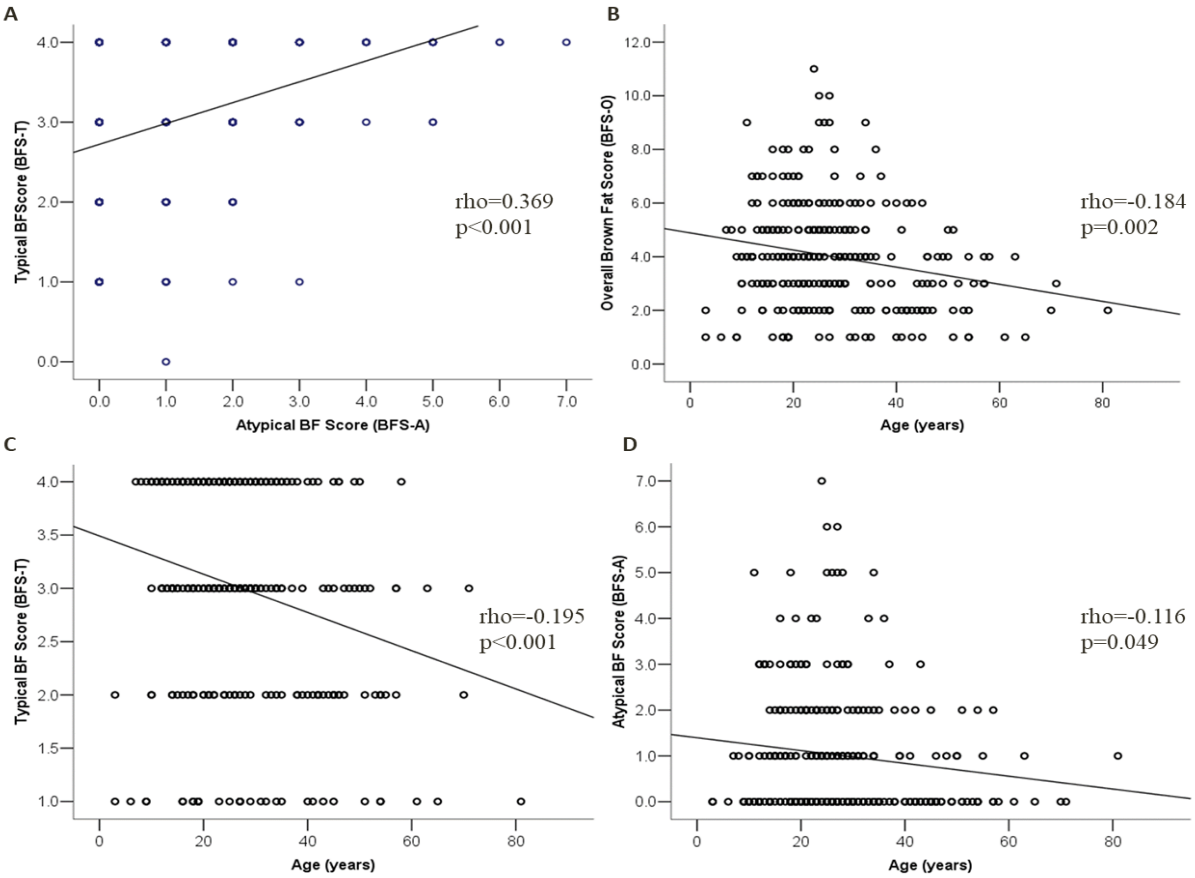


**Figure 3.** Spearman's correlation between BFS-T and BFS-A (A), and correlations between BFS-O, BFS-T & BFS-A versus patients' age (B, C, and D)

BFS-T and BFS-A were found to be positively correlated (rho=0.369; p<0.001). Age was negatively correlated with the BFS-O, BFS-T, and BFS-A (rho=-0.184; p=0.002), (rho=-0.195; p<0.001), and (rho=-0.116; p=0.049) respectively (**Figure 3**).

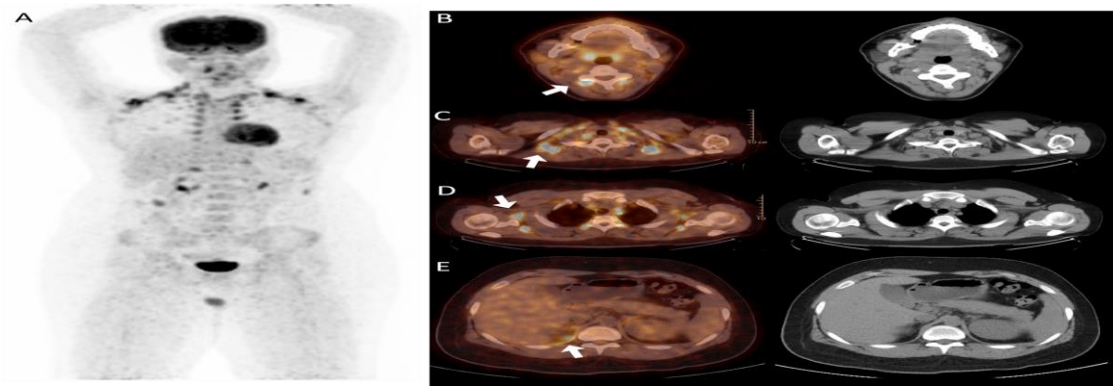


**Figure 4.** A 23 year old male patient with testicular germ cell tumor, post radical left orchiectomy and chemotherapy. Activated BAT is noted at multiple regions on MIP image (A) and fused PET/CT images (middle panel), including cervical paravertebral (B), supraclavicular (C), axillary & mediastinal (D), and right perinephric (E). The corresponding low dose CT images are displayed on the right side panel.

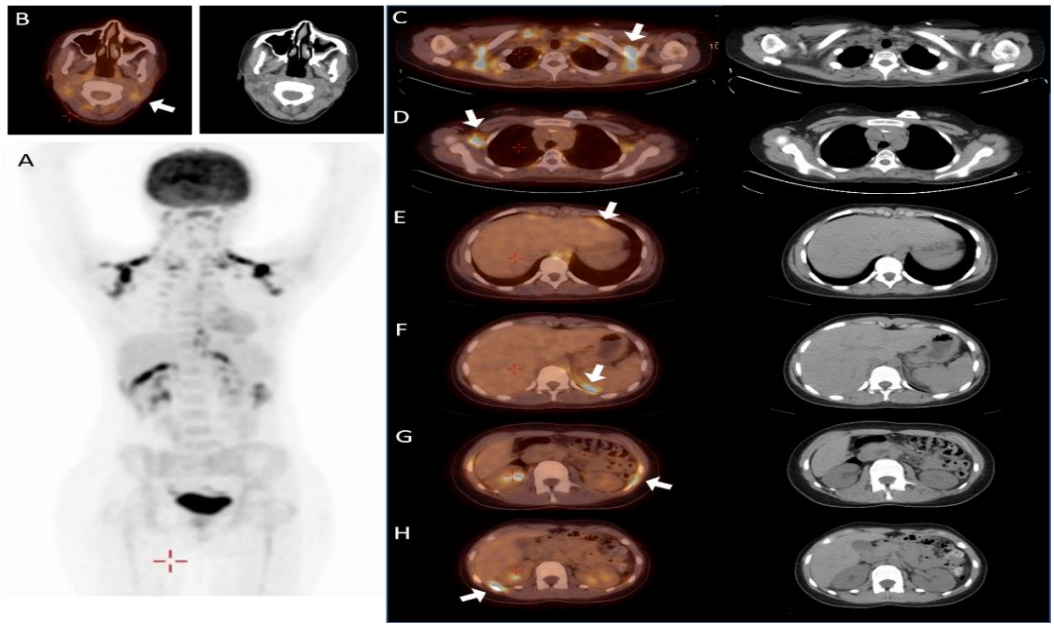


**Figure 5.** A14 year old female patient, with Hodgkin's disease, post-chemotherapy. Activated BAT is noted at multiple regions on MIP image (A) and fused PET/CT images (middle panel), including cervical (B), supraclavicular (C), axillary (D), subdiaphragmatic/perihepatic (E), left suprarenal (F), paracolic (G) and perinephric (H). The corresponding low dose CT images are displayed on the right side.

Patients with a BFS-O of >4 or those who demonstrated atypical brown fat sites were younger with a mean age of 24.29 ± 8.67 compared to 29.46 ± 14.63 ($p<0.001$) and 25.95 ± 11.31 compared to 29.26 ± 14.41 ($p=0.03$) respectively. Out of our 291 studies, 72 (25%) were for patients ≤18 years old while 224 (77%) were for patients <35 years of age. Figures 4 and 5 demonstrate 2 studies with multiple areas of brown fat activation in typical and atypical body regions.

## DISCUSSION:

The presence of activated BAT in $^{18}$F FDG-PET scans is a widely recognized issue, particularly in children and young adults. This can significantly impede the accurate evaluation of the scans[18]. PET-CT is the predominant imaging technique now employed for the examination of BAT [19-20].

Various methods for scoring BAT were present for example **Brady et al**. scored the FGD uptake of BAT as: 0 = no uptake; 1= mild uptake < liver; 2 = moderate uptake as liver; and 3 = intense uptake > liver [21]. In another work a visual grading scale comprising four levels was employed: Level 1 indicates activity below that of the liver, Level 2 denotes activity on par with the liver, Level 3 signifies activity above the liver, and Level 4 corresponds to activity as that of the brain. [13]. In this

study, we generated a simple quantitative brown fat score (BFS) for the overall brown fat (BFS-O), typical brown fat (BFS-T), and atypical brown fat (BFS-A) by summation of the number of engaged body areas in each scan to quantify the degree/extent of activated FDG avid BAT.

We found that age was significantly negatively correlated with the BFS-O, BFS-T, and BFS-A, additionally, patients with a BFS-O of >4 or atypical brown fat sites were younger; these findings were concordant with previous studies [2, 3, 22, 23-25].

The prevalence of active BAT is about 3% in males and 7.2–7.5% in females [4]. In other investigations, the female-to-male ratio was 1.74:1 and 2:1 [26]. In comparison to adults and other age groups, a study by Perkins et al. showed that in the pediatric age group, males have a higher frequency of BAT compared to females [26]. In contrast, several previously performed studies showed that BAT frequency did not differ between males and females [18, 26, 27]. About 56.9 % of our study population are females, however, our study model is not designed and is probably not appropriate to accurately assess BAT prevalence. Moreover, in the current study, we found no statistically significant differences in mean BAT scores between males and females.

PET/CT studies of the BAT show moderate to high uptake of FDG, which is usually found in the lower neck, supraclavicular areas, and along the thoracic cost-vertebral junctions [28-30]. In our study, brown fat was classified based on the sites implicated as either typical or atypical with the typical sites more frequently seen and generally more superficial in location while the atypical sites are less frequently seen and more deeper in location. Active brown fat was found 99.7% of the time, in the supraclavicular, cervical, axilla, and paravertebral areas. This is similar to what other studies have found [22, 31]. In the current study, supraclavicular regions were the most frequent sites to show activated BAT, concordant to previous studies that showed the same findings [32, 33]. We found that the atypical BAT sites were activated less frequently (50.5%) and were generally deeper in location. In order of decreasing frequency, these sites are the abdominal paraaortic, mediastinal, peri hepatic, suprarenal, subscapular, para colic, retro crural, perinephric, para-psoas, pericardial and subpectoral regions; this was in line with the results of **Lietner et al** [34].

Physical and chemical stimuli, such as cold, heat, immobility, radiation, noise, pain and emotional stress, have the potential to induce sympathetic nervous system stimulation, inducing BAT activation [35]. Several studies reported that the prevalence of BAT detection is influenced by the outdoor temperature, being more frequent with decreasing temperatures and less with increasing temperatures [36-38]. Also, **C.Pötzsch** et al, concluded that warming can reduce BAT activation, though such inhibitory effect is attenuated with increasing outdoor temperatures[18]. **Kim et al.** concluded that the increased FDG uptake in BAT occurs more often as an

acute response to cold weather (1-7 days) rather than to prolonged periods of average cold weather [36].

Our study considers the effect of temperature in different seasons, and the average weather in Riyadh, Saudi Arabia, is utilized to divide the year into two distinct seasons. The hot season extends for seven months (start of April to the end of October), whereas the cold season spans five months (start of November to the end of March). We found that there is a substantially higher number of studies with activated BAT during the hot season tah during the cold season (182 versus 109; $p<0.001$). Moreover, the mean BFS-O and BFS-A were significantly higher in the cold season than in the hot season of the year (4.2 compared to 3.6; $p=0.004$) and (1.2 compared to 0.7; $p<0.001$), respectively which is in line with the previously mentioned studies [36-38]. **Gerngroß et al**. also studied the effect of German weather (**Deutscher Wetterdienst**) on BAT activation and found that the occurrence of BAT-positive scans exhibits a seasonal trend, demonstrating reduced frequency during the summer season [13] similar to previous studies [23, 38, 39].

We believe that studying $^{18}$F FDG avid activated BAT, not only regarding site but concerning time as well, due to seasonal temperature variations for each particular climate zone, is important for a better understanding of BAT physiology, extent, and variations in its glucose metabolism. This may have important implications on the interpretation of $^{18}$F FDG studies and probably may provide valuable clinical information, based on previous studies linking the presence of BAT to various medical conditions such as obesity and metabolic diseases.

## STUDY LIMITATIONS:

The study has several limitations. Firstly, the text search used to retrieve studies with activated BAT had likely failed to recognize a lot of studies in which the presence of brown fat was not mentioned in their reports. We believe this led to an underestimation of brown fat prevalence in the study. Secondly, since activated BAT is much more prevalent during the cold season of the year, the summer months (July-August) are represented by BAT scores of only a few studies. Thirdly, the brown fat scores were calculated by simply adding up the number of affected regions in each patient, without considering the exact volume of affected adipose tissue or the intensity of FDG metabolic uptake in each region. This method allowed for an approximate estimation of the brown fat extent, though it may not accurately reflect the intensity of metabolic activity as in metabolic volume assessment. Fourthly, the BAT was classified as typical and atypical based on the frequency of detection of BAT in different sites with atypical sites being less frequent and more variable. Given this significant variability, we believe that atypical BAT sites are likely not restricted to the sites documented in the current study and may greatly differ among diverse individuals and

populations. Fifthly, we did not investigate the relationship between activated BAT patterns or extent and other factors as associated comorbidities (e.g. diabetes, obesity, etc..) or prior therapies or medications. Lastly, the results of the current study may not apply to other patient populations of a different ethnicity or geographic location with different climate or seasonal temperature changes.

## CONCLUSIONS:

Both typical and atypical brown fat locations have been identified. When active brown fat is observed, it is almost always observed in one or more typical sites, whereas deeper atypical sites are observed in a minority of patients with extensive brown fat activation and are rarely observed if the more superficial typical sites are not affected. Colder seasons and younger ages were associated with more frequent and more extensive BAT activation and more frequent atypical BAT site detection. The study provides a mapping for activated BAT that could be helpful for the interpretation of FDG PET/CT studies.

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