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Original Article

Correlation of Cancer Status and Brown Adipose Tissue Activity on 18F-Flourodeoxyglucose positron emission tomography/computed tomography

18F-Fluorodeoksiglukoz positron emisyon tomografi/bilgisayarlı tomografi'de kahverengi yağ dokusu aktivitesi ve kanser durumunun korelasyonu

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ABSTRACT

Aim: In this study, we aimed to compare brown adipose tissue (BAT) activity on 18F-Flourodeoxyglucose Positron Emission Tomography (PET)/Computed Tomography(CT) in patients with and without active cancer.

Material and Methods: Results of the patients who underwent 18F-FDG PET/CT between January 2014 and February 2018 in Nuclear Medicine Department were evaluated retrospectively. Age, gender, body mass index (BMI), serum levels of glucose, bilirubin, total cholesterol (T-chol), low-density lipoprotein (LDL) and triglyceride (TG) of the patients were noted from the hospital database. Mean outdoor temperature of the day during PET/CT imaging was searched from National Weather Service archives. Diagnosis and disease activity status on PET/CT imaging were evaluated retrospectively. Standardized uptake value (SUV) and brown adipose tissue volume (BAV) were calculated on PET/CT images. Additionally, hepatic attenuation index and subcutaneous adipose tissue thickness (SCATT) were calculated from CT images. Difference between median SUV and BAV among groups with and without active cancer was analyzed.

Results: Totally 78 (54 F; 24 M; mean age 34.4±15.6) patients who underwent 18F-FDG PET/CT for different oncological indications were included in the analysis. All the patients had different degrees of BAT uptake on PET/CT images. Median (min-max) values for SUV, BAV and SCATT were found as 8.0 (2.7-37.0), 26.9 (2.1- 116.0) cm3 and 15.0 (3.0- 46.0) mm, respectively. Hepatic attenuation index was 0-5%, 6-30% and >30% in 56 (71%), 20 (26%) and 2 (3%) patients, respectively. Active disease was observed in 26 (33%) patients during PET/CT imaging. In the evaluation of the distribution of the adipose tissue parameters, median SUV (p=0.008) and BAV (p=0.008) of groups with and without active cancer were found statistically significant.

Conclusion: BAT activity in patients with active cancer seems to be higher than that in patients without active disease, supporting the possible role of adipose tissue activation on cancer development and progression.

Keywords: Brown adipose tissue; positron emission tomography; Fluorodeoxyglucose F18.

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ÖZ

Amaç: Bu çalışmada 18F-Fluorodeksiglukoz (FDG) positron emisyon tomografi/ bilgisayarlı tomografi (BT)'de aktif kanseri olan ve olmayan hastalarda kahverengi yağ dokusu (KYD) aktivitesinin kıyaslanmasını amaçladık.

Gereç ve Yöntemler: Ocak 2014-Şubat 2018 tarihleri arasında kliniğimizde tüm vücut 18F-FDG PET/BT çekilen hastaların raporları hastane kayıtlarından araştırıldı. Yaş, cinsiyet, vücut kitle indeksi (VKİ), kan glukoz, bilirubin, total kolesterol (T-kol), düşük dansiteli lipoprotein (LDL) ve trigliserit (TG) düzeyleri not edildi. PET/BT görüntülemesi sırasında ortalama dış mekan hava sıcaklığı internetten araştırıldı. Tanı ve PET/BT sırasında hastalık aktivitesi hastane kayıtlarından araştırıldı. Standardize uptake değeri (SUV) ve kahverengi yağ dokusu volümü (KYV) PET/BT görüntülerinden hesaplandı. Ek olarak hepatic atenüasyon indeksi ve subkutan yağ dokusu kalınlığı (SKYDK) BT görüntülerinden hesaplandı. Aktif kanseri olan ve olmayan gruplar arasında median SUV ve KYV farkları analiz edildi.

Bulgular: Çeşitli onkolojik endikasyonlarla 18F-FDG PET/BT çekilen toplam 78 hasta (54 K; 24 E; ortalama yaş 34.4±15.6) çalışmaya dahil edildi. Her hastanın PET/BT görüntülerinde farklı KYD tutulumu vardı. SUV, KYV ve SKYDK için median değerleri sırasıyla 8.0 (2.7-37.0), 26.9 (2.1- 116) cm3 and 15.0 (3.0- 46.0) mm olarak bulundu. Hepatosteatoz indeksi 56 hastada (%71) %0-5, 20 hastada (26%) %6-30 ve 2 hastada (3%) >%30 idi. 26 hastada (33%) PET/BT görüntüleme sırasında aktif hastalık mevcuttu. Kahverengi yağ dokusu parametrelerinin gruplar arasında dağılımının incelemesinde, aktif kanseri olan ve olmayan hastalarda median SUV (p=0.008) ve KYV (p=0.008) değerleri arasında anlamlı farklılık bulundu.

Sonuç: Kanser gelişimi ve progresyonununda kahverengi yağ dokusu aktivasyonunun muhtemel rolünü destekler nitelikte olmak üzere, aktif kanseri olan hastalarda, olmayanlara göre KYD aktivitesi daha yüksek görünmektedir.

Anahtar Kelimeler: kahverengi yağ dokusu; positron emisyon tomografi; florodeoksiglukoz F-18.

Introduction

Brown adipose tissue is primarily responsible for the protection of the body temperature of mammals and is activated by sympathetic nervous system [1]. Cold exposure increases BAT activity [2]. BAT consumes high amounts of glucose and fatty acid [3, 4]. It is known that BAT mass has a negative association with total fat mass, visceral adipose tissue (VAT) and subcutaneous adipose tissue [5-8]. Moreover, high levels of BAT are associated with cancer related cachexia [9].

Adipocyte-derived factors have been demonstrated to stimulate or inhibit cell growth [12]. For this reason, the link between obesity and cancer has been a subject of interest. Recently BAT has gained interest in the development of cancer [13-15]. Animal studies have shown that activation of BAT has a role in the synthesis and activation of angiogenic and growth factors [16-17]. Moreover, recent studies have shown that BAT may play a role in the development and progression of cancer [10-11].

18F- FDG PET/CT is a widely used modality in staging and restaging of various types of cancers [18, 19]. Because of its high glucose consumption, BAT might be quantified by 18F-FDG PET/CT imaging [20]. In the literature, limited number of studies have been reported in the evaluation of BAT by 18F FDG PET/CT and cancer activity [21-23].

In this study, we aimed to compare the degree of BAT activity on 18F-FDG PET/CT in patients with and without active cancer detected by 18F-FDG PET/CT.

Material and Methods

Patients

Following ethics committee approval (2021/103), 18F-FDG PET/CT reports of patients who underwent whole body PET/CT between the dates of January 2014 and February 2018 were collected from the hospital database. The indications for PET/CT study were either staging, restaging or assessment of treatment response. Only patients with visually evident and measurable BAT uptake were included in the study. BAT uptake was reported in a total of 121 patients. Forty patients were excluded from analysis because their blood test results or PET/CT images were not available and three hyperthyroid patients were excluded because of the possible effect of thyroid hormones on BAT activity. Age, gender, body mass index (BMI), serum levels of glucose, bilirubin, T-chol, LDL and TG levels of patients were noted for analysis. Mean outdoor temperature of the day during PET/CT imaging was acquired from the National Weather Service archives. Diagnosis and disease activity during PET/CT imaging were searched from hospital database. Findings of 18F-FDG PET/CT, other imaging modalities and serum tumor marker measurements were used to confirm disease activity.

18F-FDG PET/CT imaging

Whole-body PET/CT images were acquired with a Discovery PET/CT 710 series scanner (General Electric, Milwaukee, USA) 60 minutes after injection of 8-10 mCi 18F-FDG. Serum glucose levels were confirmed to be <150mg/dL following 6 hours fasting, before radiopharmaceutical injection. Images from the vertex to the proximal femur were obtained while patients were in the supine position. PET images were acquired for 2 min per bed position. PET images were reconstructed with non-contrast low-dose CT images that were obtained with the use of a standardized protocol of 120 kV, 70 mA, tube rotation time of 0.5 s per rotation, a pitch of 1.375, and a slice thickness of 3.3 mm. Patients were allowed to breathe normally during the procedure. Standardized uptake value (SUV) and BAV were calculated by using VCAR software of Advanced Workstation (General Electric, Milwaukee, USA) (Figure 1).

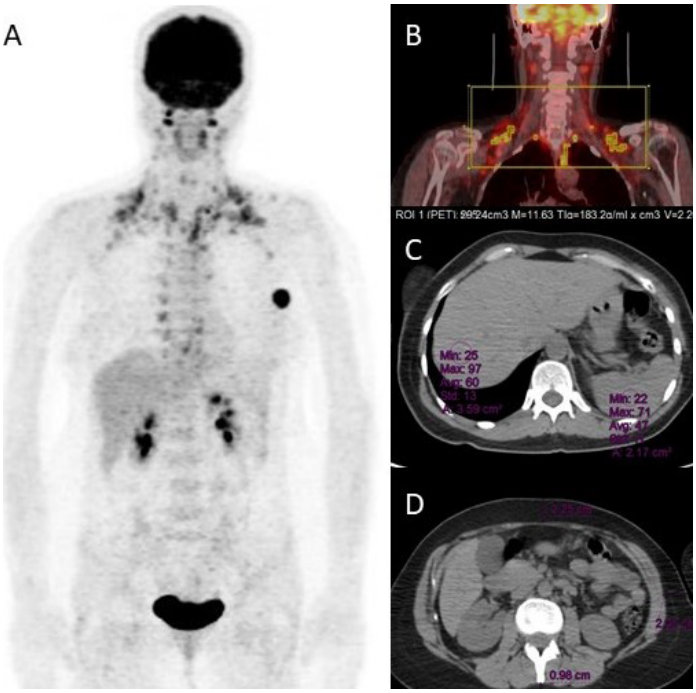

Figure 1: Maximum intensity projection image of whole body 18F-FDG PET study with an intense 18F-FDG uptake in the neck and supraclavicular region symmetrically (A). Coronal PET/CT fusion image of the neck and upper thorax demonstrating the region of interest drawn over the 18F-FDG avid brown adipose tissue with the given threshold and automatically calculated quantitative indices (B). Regions of interests drawn to calculate hepatic and splenic attenuation index (C) and subcutaneous adipose tissue thickness at L3 vertebra level (D).

Additionally, hepatic attenuation index and SCATT were calculated from CT images. A blinded reviewer studied non-contrast PET-CT scans to determine the amount of SCATT. The SCATT was measured at L3 level which included an anterior (distance from linea alba to skin), posterior (distance from tip of spinous process of vertebrae to skin), and lateral (external oblique or serratus anterior fascia to skin) measurement and mean abdominal adipose tissue thickness was calculated from these three measurements (Figure 1).

Hepatic attenuation index was calculated in order to determine the degree of hepatic steatosis. Mean hepatic and splenic attenuation was calculated by averaging 25 region-of-interest (ROI) measurements on five sections (five ROIs per section). Hepatic attenuation index (HAI) was derived and defined as the difference between mean hepatic and mean splenic attenuation. HAI greater than 5 Haunsfield Unit (HU) correlated with macrovesicular steatosis of <5%. The HAI between -10 and 5 HU correlated well with macrovesicular steatosis in the mild-to-moderate range of 6%–30%. The HAI of less than -10 HU correctly predicted steatosis greater than 30% (Figure 1).

Data and Statistical Analyses

Patient grouping was made according to existence of active cancer disease on PET/CT. Thus, patients were divided into two groups as PET positive (patients with active cancer disease according to pathological findings on PET/CT) and PET negative patients (patients with no pathological uptake indicative of active cancer disease on PET/CT). Median values of SUV, BAV, SCATT and Hepatic attenuation index were compared between these two groups: Patients with active cancer disease on 18F-FDG PET/CT and patients with no signs of active cancer disease on 18F-FDG PET/CT.

Differences of continuous parameters between groups were evaluated by using independent samples T test. Significance levels was set as a P value <0.05. SPSS 21 (IBM Corporation, Armonk, North Castle, NY) was used for statistical analysis.

Results

Totally 78 (54 F; 24 M; mean age 34.4±15.6) patients who underwent 18F-FDG PET/CT for different oncological indications were included in the analysis. All patients had different degrees of BAT uptake on PET/CT images. BMI of patients ranged between 14 and 34 with a median value of 22. Median (min-max) values for outdoor temperature, blood glucose, T-chol, LDL, TG, TSH levels were calculated as 2 (-10-24)°C, 87 (79-145) mg/dL, 175 (118-331) mg/dL, 104 (56-244) mg/dL, 105 (38-598) mg/dL, 2.0 (1-4) mIU/L. Details of patient characteristics are given in Table 1.

Table 1: Details of patient group.

	BMI (kg/m2)	Age (years)	outdoor temperature (°C)	Fasting glucose level (mg/dl)	T-chol (mg/dl)	TG (mg/dl)	LDL (mg/dl)	TSH level (mIU/L)	SUV	BAV (cm3)	SCAT thickness (mm)
Mean	22.7	34.42	4	89	183.39	134.98	111.62	3.9	10	34	17.4
Median	22.5	33.5	2	87	175	105	104	2.1	8	26.9	15
Std. Deviation	4.3	15.56	8.3	14.1	41.7	99.9	36.28	11.24	6.3	24.3	10.2
Minimum	14	9	-10	79	118	38	56	0.4	2.7	2.1	3
Maximum	34	81	24	145	331	598	244	100	37	116	46

BMI:Body mass index, T-chol: total cholesterol, TG: triglyceride, LDL: low density lipoprotein, TSH: thyrotropin releasing hormone, SUV: standardized uptake value, BAV: brown adipose tissue volume, SCAT: subcutaneous adipose tissue.

Median (min-max) values for SUV, MTV and SCATT were found as 8.0 (2.7-37.0), 26.9 (2.1- 116) cm3 and 15.0 (3.0- 46.0) mm, respectively. Hepatic attenuation index was 0-5%, 6-30% and >30% in 56 (71%), 20 (26%) and 2 (3%) patients, respectively. Active disease was observed in 26 (33%) of patients during PET/CT imaging. Details of the active disease rates based on the diagnosis were given in Table 2. There was no significant difference between clinical characteristics of patient groups with or without active cancer. Summary of the data of clinical characteristics of patient groups were given in Table 3.

In the evaluation of the distribution of adipose tissue parameters between groups, the difference between median values of SUV and BAV of groups with and without active cancer was found statistically significant. Difference of median values of SCATT and hepatic attenuation index between groups was not significant. Summary of the distribution of adipose tissue parameters of groups with and without active cancer is given in Table 4.

Table 2: Patients with and without active cancer according to diagnosis.

Cancer type	No active cancer n=52	Active cancer n=26	Total n=78
Hematological malignancies	25	7	32
Gynecological malignancies	3	1	4
Sarcoma	11	3	14
Head and neck cancers	3	2	5
Lung	0	4	4
Primary unknown tumor	1	0	1
Urological tumors	2	1	3
Gastrointestinal tumors	2	1	3
Breast	5	7	12

Table 3: Clinical characteristics of patients.

Variable	No active cancer (n=52)	Active cancer (n= 26)	P value
Age (years)	31.0	38.0	0.9
F/M	35/17	19/7	0.6
Outside temperature (°C)	1.0	4.0	0.7
Fasting glucose level (mg/dl)	87.0	89.0	0.6
BMI (kg/m2)	22.0	24.0	0.6
TSH (mIU/L)	2.4	1.7	0.9

F: female, M: male, BMI:Body mass index, TSH: thyrotropin releasing hormone.

*Data are presented as median values for continuous variables.

Table 4: Distribution of adipose tissue parameters of groups with and without active cancer.

Variable	No active cancer (n=52)	Active cancer (n= 26)	p
SUV	7.1	12.2	0.008
BAV (cm3)	21.0	44.1	0.008
SCAT thickness (mm)	15.0	17.0	0.80
Hepatosteatosis index	1.0	1.0	0.60

SUV: standardized uptake value, BAV: brown adipose tissue volume, SCAT: subcutaneous adipose tissue.

*Data are presented as median values for continuous variables.

Discussion

Relationship between adipose tissue and development of cancer has been an emerging topic in recent years. It is known that obesity is linked to an increased risk of cancer [24-26]. However, association between BAT and cancer is not proven clearly. Two types of BAT are classified. The first one arises from muscular lineage stem cells and called as "classical brown adipocytes". The second type derives from white adipose stem

cell lineage and known as "beige adipose cells". Beige cells can transform within the white adipose tissue and this process is known as browning [27, 28]. Normally in adults, BAT is located in the neck, supraclavicular and paravertebral regions and has a mixture of brown and beige adipocytes [29, 30].

Uncoupling protein 1 (UCP-1) is responsible for the browning of white adipose tissue [31]. In a mice model, UCP-1 mRNA levels in the BRCA1 mutant mice have been found 50-fold elevated in the comparison of wild-type mice. In a similar model, increased vascularity and angiogenesis was demonstrated. Authors concluded that there might be a relationship between BAT activity and tumor angiogenesis [32]. To support the possible role of BAT activity in the development of breast cancer, Cao et al searched the link between BAT and breast cancer in 96 breast cancer patients. They found a higher prevalence of BAT compared to the other malignancies [21]. In this study, no comparison of prevalence of BAT on the malignancies was made, since only BAT positive patients were included in the evaluation. However, distributions of SUV and BAV between patients with breast cancer and other malignancies was not different.

In a large series, Haung et al examined the relationship between BAT activity and neoplastic status. They evaluated 1740 patients and compared the patients with and without activated BAT. In their analysis, wider BAT distribution and total metabolic activity was found in patients with a cancer history [23]. Recently, Bos et al reported their series of 142 patients with BAT uptake on PET/CT and cancer activity. BAT activity was found greater in patients with active cancer compared to those without [22]. In our analysis, similarly we found higher SUV and BAV in patients with active cancer compared to BMI, gender, age, matched BAT positive patients without active cancer. It is well known that cachexia is common in advanced stage cancer patients and related is related with poor prognosis (REF1-3). The transformation of white adipose tissue to BAT and BAT activation due inflammation is suggested a reason for cancer related cachexia [33-37]. Confirming this hypothesis, the prevalence of BAT has been found higher in patients with cachexia than age-matched controls in the light microscopic examination of necropsy specimens of periadrenal tissue [9]. Concerning these evidences, we think that transformation of white adipose tissue to BAT can be proposed as the reason for increased BAV in our patients. This may also explain why SCATT and hepatic attenuation index were not found different among patients with active and non-active cancer status. SCATT is a parameter which was proposed to reflect total body fat composition and amount of white adipose tissue in the body [38]. It is decreased in cancer associated cachexia in advanced stage patients due to transformation of white adipose tissue to brown adipose tissue. It was also expected to be decreased in patients with active cancer because median BAV and SUV values were increased. However, in this study we didn't find a statistically significant difference between median values of SCATT in patients with and without active cancer. Hepatic attenuation index is a measure of hepatic steatosis which usually takes place in cancer associated cachexia [39,40]. Hepatic attenuation index can be increased in patients with advanced stage disease, but it was not found increased in patients with active cancer. Thus, only the volume and metabolic activity status of brown adipose tissue was found higher in existence of active cancer. None of the CT parameters were associated with activity of disease.

It is obvious that various complicated reasons contribute to active disease status in cancer. Although in this study BAT activity is found to be higher in active cancer disease, no direct causal relationship can be put forward relying on the existing data. Further preclinical and clinical investigations are needed to prove this possible molecular pathway triggering cancer activation. Different parameters can affect BAT activity. Beta adrenergic activation due to stress or low blood sugar can be a reason for browning white adipose tissue [41]. Other physical and chemical stressors such as cold, heat, radiation might cause sympathetic activation [42]. BAT activity also has been shown significantly higher in younger, leaner, in female patients [23]. For this reason our patient groups were evaluated in terms of these parameters, in order to avoid a bias for BAT activity but no significant differences were detected between the two groups. We showed that the patient groups with and without active cancer are similar for these factors.

The major limitations of our study are the retrospective study design and inclusion of limited number of patients. Heterogeneity of the types of cancer can be considered as another limitation. Despite these limitations, our results might be important regarding the growing interest in BAT activity and cancer development and the limited number of studies under this topic. Further clinical studies including biochemical and genetic investigations in large series are needed to achieve a definite conclusion.

Conclusion

Supporting the possible role of the adipose tissue activation on the cancer development, BAT activity in patients with

active cancer seems to be higher than those without. The transformation of white adipose tissue to brown adipose tissue may play a role in increased BAT activity and BAV.

Declaration of conflict of interest

The authors received no financial support for the research and/or authorship of this article. There is no conflict of interest.

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