



The Relation Between the Blood Glucose Level and the FDG Uptake of Tissues at Normal or Near-Normal PET/CT Imaging

Normal veya Normale Yakın PET/BT Görüntülerinde Kan Glukoz Düzeyi ile Dokulardaki FDG Uptake Arasındaki İlişki

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ABSTRACT

Objective: The aim of this study was to evaluate the relation between the blood glucose level and 18F-FDG uptake in tissues at normal or near-normal PET/CT examinations.

Material and Methods: Patients with newly diagnosed cancer who underwent 18F-FDG PET/CT for initial staging were evaluated retrospectively. Sixty five patients (47 female, 18 male) with a normal or near normal FDG distribution were included this study. Mean standardized uptake value of the brain, heart, lung, mediastinum, pancreas, liver, spleen, skeletal muscle and bone marrow were calculated. Blood glucose levels measured immediately prior to administration of FDG were used.

Results: There was a statistically significant positive correlation between the blood glucose level and liver and muscular FDG uptake. Brain FDG uptake value was negatively correlated with the glucose level. There was no correlation between the blood glucose level and other tissues' FDG uptake values. The patients with increased blood glucose levels showed significantly higher muscular and lower brain FDG uptake compared with patients with normal glucose levels.

Conclusion: Effect of hyperglycemia during 18F FDG PET/CT imaging on normal tissues is variable. While skeletal muscle and brain are the most affected tissues, the liver is slightly affected in a clinically insignificant manner.

Key Words: Fluorodeoxyglucose, Positron emission tomography/computerized tomography, hyperglycemia, blood glucose

ÖZ

Amaç: Bu çalışmanın amacı, normal veya normale yakın PET/BT görüntülerinde dokulardaki 18F-FDG tutulumunun kan glukoz düzeyi ile ilişkisini değerlendirmektir.

Gereç ve Yöntemler: Yeni kanser tanı almış ve ilk evreleme amacıyla 18F-FDG PET/BT yapılan hastalar geriye dönük olarak değerlendirildi. Normal veya normale yakın FDG dağılımı olan 65 hasta (47 kadın, 18 erkek) çalışmaya dahil edildi. Beyin, kalp, mediasten, pankreas, dalak, iskelet kası ve kemik iliği ortalama standardize uptake değerleri ölçüldü. FDG enjeksiyonundan hemen önce ölçülen kan glukoz düzeyleri değerlendirmede kullanıldı.

Bulgular: Kan glukoz düzeyi ile karaciğer ve kas FDG tutulum düzeyleri arasında istatistiksel anlamlı pozitif korelasyon vardı. Beyin FDG tutulumu glukoz düzeyi ile negatif olarak korele idi. Diğer dokulardaki FDG tutulumu ile kan glukoz düzeyi arasında ilişki yoktu. Kan glukoz düzeyi yüksek olan hastalar, normal kan glukoz düzeyi olan hastalardan daha yüksek kas ve daha düşük beyin FDG tutulumu gösterdi.

Sonuç: 18F-FDG PET/BT görüntülerinde hipergliseminin normal dokularda etkisi değişkendir. İskelet kası ve beyin en çok etkilenen dokular iken, karaciğer klinik olarak önemsiz şekilde daha düşük oranda etkilenmektedir.

Anahtar Sözcükler: Florodeoksiglukoz, Pozitron emisyon tomografi/bilgisayarlı tomografi, hiperglisemi, kan glukoz

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INTRODUCTION

18F-2-deoxy-2-fluoro-D-glucose (FDG), a glucose analogue, is the standard tracer used to evaluate neoplastic tissue during positron emission tomography and computed tomography (PET/CT) examinations. The standardized uptake value (SUV) is a semiquantitative parameter used to measure tracer accumulation in tissues (1). Hyperglycemia impairs the tumor FDG uptake because of competition with blood glucose (2-4). According to the guidelines, blood glucose should be measured prior to PET/CT imaging, and the examination should be rescheduled whenever the value exceeds 200 mg/dL (5,6). The plasma glucose level has a major influence on SUVs but no clear consensus on the real impact of glycemia on 18F-FDG uptake as regards the effects of blood glucose levels on SUVs in different organs exists (7,8). Some studies have concluded that hyperglycemia reduces brain FDG uptake that could mimic patterns seen in some dementia disorders (9). Liver and mediastinal blood pool are the commonly used background tissues for the assessment of treatment response and glycemic fluctuations may lead to incorrect evaluation of therapy response. Additionally, increased uptake by surrounding normal tissues may cause misinterpretation of pathological lesion during PET/CT studies.

The aim of this study was to evaluate the relationship between the blood glucose level and 18F-FDG uptake in normal tissues during normal or near-normal PET/CT examinations.

MATERIALS and METHODS

Study Design

All patients with newly diagnosed cancer who had undergone 18F-FDG PET/CT for initial staging from January 2017 to September 2018 were evaluated retrospectively. Patients who had been exposed to chemotherapy or radiotherapy prior to imaging were excluded. Imaging with normal or near-normal FDG distributions such as small hypometabolic lung lesions, reactive normal-sized lymph nodes with mildly increased uptake, and weak uptake in surgical scars were included in this study. Patients with increased FDG uptake on tissues associated with non malignant causes such as diffuse bone marrow FDG uptake or lung infection were excluded.

A total of 65 patients (47 female, 18 male) aged 22-82 years (average \pm SD: 58.8 \pm 13 years) were included in the study. Eighteen of these patients were diabetic and were on antidiabetic treatment. The primary diagnoses were as follows; breast cancer (n=32), lung cancer or solitary pulmonary nodule (n=7), colorectal cancer (n=6), urogenital tumor (n=9), larynx (n=1), stomach (n=1), multiple myeloma (n=1), pancreas (n=2), lymphoma (n=1),

skin (n=2), primary unknown cancer (n=2) and sarcoma (n=1).

F-18 FDG PET/CT Imaging

The blood glucose level was measured using the same glucometer immediately prior to the administration of FDG. All patients' fasting blood glucose levels were less than 200 mg/dL prior to imaging (80-198 mg/dL, average \pm SD: 108 \pm 29 mg/dL). After intravenous administration of 270-370 MBq of 18F-FDG, the patients rested in a quiet room. Oral contrast was given to all patients. Whole body imaging was performed after a resting period of 60 minutes using a Siemens (Biograph mCT) PET/CT scanner. The CT scan data were collected at 120 kV and 50 mAs. The PET acquisition was performed from the head to upper thighs or foot at a rate of 2 minutes per frame.

For semi-quantitative evaluation, elliptical volumes of interest (VOIs) of different sizes adapted to the various organs/tissues were drawn using the fused transaxial PET/CT images. To minimize the impact of an inhomogeneous distribution of tracer, mean standardized uptake value (SUV_{mean}) was preferred to maximum standardized uptake value (SUV_{max}). SUV_{mean} of the brain was calculated by 4.0-5.0 cm³ volume at the right parietal lobe and right cerebellum. There was a correlation between these uptake values as a result of the correlation analysis (r: 0.803, p <0.01) and parietal lobe uptakes were used for the statistical evaluation. SUV_{mean} of the lung was assessed by VOI with a volume of 5.0-10 cm³ in the right lung. Mediastinum SUV_{mean} was calculated with a volume of 4.0-5.0 cm³ in the lumen of a large mediastinal vessel (aorta). SUV_{mean} of the liver was calculated by VOI with a volume of 20-30 cm³ in the right lobe of the liver. Pancreas and spleen VOI's were calculated similarly by VOI's with 4 to 8 cm³ in various parts of organs. Bone marrow SUV_{mean} was assessed by VOI's in the right iliac crest, the 5th lumbar vertebrae and the right proximal femur. There was a correlation between these uptake values as a result of the correlation analysis (r: 0.575, r: 534 and r: 673 p <0.01) and iliac crest uptakes were used for the statistical evaluation. Muscular SUV_{mean} was calculated by VOI's with 20-30 cm³ volume in both the right psoas and gluteal muscles. Due to the strong correlation between these values (r: 0.410, p <0.01), gluteal muscle uptake values were used for the statistical evaluation.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) version 18.0. The correlation between semiquantitative values of tissues and blood glucose levels were analyzed by Spearman's rank correlation test. The "Independent samples t-test" and "Mann-Whitney U test" were used for the comparison

of groups. P values <0.05 were considered statistically significant.

RESULTS

There was a statistically significant negative correlation between blood glucose levels and brain FDG uptake values (r: -585, p<0.01) (Figure 1). There was also a positive correlation between blood glucose levels and muscle (r: 359, p<0.01) (Figure 2) and liver (r: 246, p<0.05) FDG uptakes. Lung, mediastinum, myocardium, pancreas, spleen, and bone marrow FDG uptake values were not correlated with blood glucose levels (p>0.05). Detailed statistical results are shown in Table I. Blood glucose levels were higher than 110 mg/dL in 21 patients. When comparing the patients with normal blood glucose (<110 mg/dL) with the increased ones (≥110 mg/dL), statistically significantly higher

muscular uptake and lower brain uptake were detected in the patients with high glucose levels (Table II).

DISCUSSION

Cellular glucose uptake is a complex mechanism. Like glucose, FDG transfer into the cells is mediated by the glucose transporters (GLUT) 1 to 7 and the sodium-glucoselinked transporters (10). The brain demonstrates the highest physiological FDG uptake due to its high glucose metabolism. However, sometimes FDG uptake of the brain is abnormally low, even in the absence of a brain disease. Hyperglycemia at the time of the FDG PET/CT examination is one of the causes of reduced brain FDG uptake (11). Insulin increase and subsequent GLUT activation is a normal response to hyperglycemia. Insulin resistance leads to decreased GLUT 1 and 3 expression

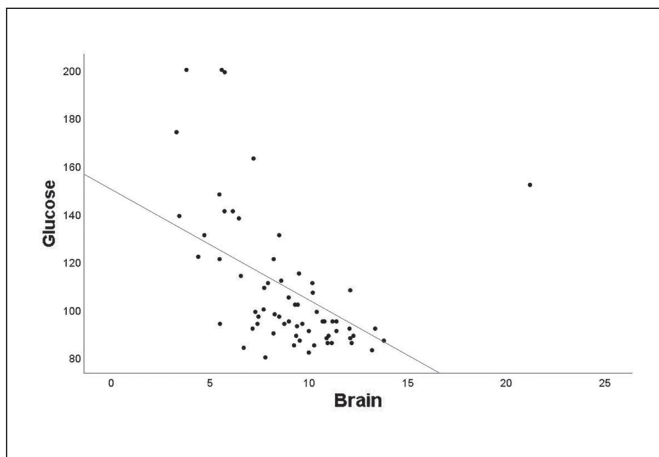


Figure 1: Negative correlation between blood glucose levels (mg/dL) and brain FDG uptake (r: -585, p<0.01).

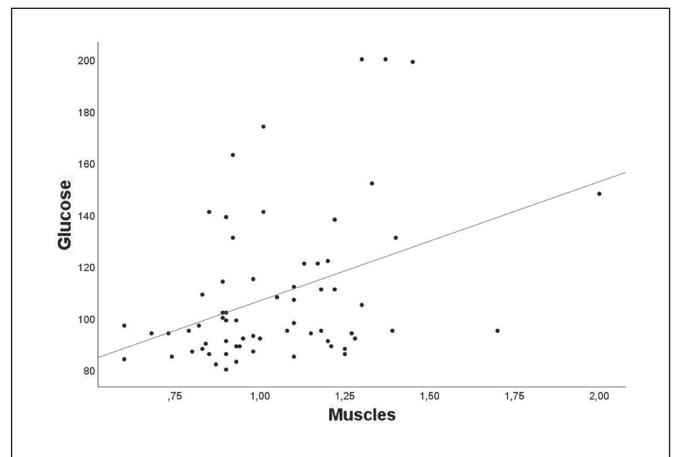


Figure 2: Positive correlation between blood glucose levels (mg/dL) and skeletal muscle FDG uptake (r: 359, p<0.01).

Table I: Results of Spearman’s correlation between blood glucose and SUVmean of various normal tissues at FDG PET/CT imagins.

| | Brain | Lung | Mediastinum | Heart | Liver | Pancreas | Spleen | Bone marrow | Muscle |
|---------------|--------------|-------------|--------------------|--------------|--------------|-----------------|---------------|--------------------|---------------|
| Blood glucose | -0.585** | 0.068 | 0.127 | -0.55 | 0.246* | -0.074 | 0.208 | 0.220 | 0.359** |
| p | 000 | 0.589 | 0.312 | 0.666 | 0.048 | 0.555 | 0.105 | 0.078 | 0.03 |

*p<0.05, **p<0.01.

Table II: Mean SUVmean (±SD) of various tissues in patients with normal and high blood glucose level.

| | Brain | Lung | Mediastinum | Heart | Liver | Pancreas | Spleen | Bone marrow | Muscle |
|-----------------------------|--------------|-------------|--------------------|--------------|--------------|-----------------|---------------|--------------------|---------------|
| Normal blood glucose (n=44) | 9.8±1.9 | 0.8±0.4 | 2.3±0.5 | 4.2±2.3 | 2.9±0.4 | 2±0.4 | 2.4±0.3 | 1.6±0.6 | 0.9±0.3 |
| High blood glucose (n=21) | 7±3.7 | 0.8±0.2 | 2.3±0.4 | 3.5±1.6 | 3.1±0.5 | 2±0.3 | 2.8±0.5 | 1.8±0.4 | 1.2±0.2 |
| p | 0.000 | 0.927 | 0.982 | 0.337 | 0.117 | 0.803 | 0.127 | 0.062 | 0.005 |

and compatible glucose uptake in the brain. Similar to prior studies, cerebral cortical FDG uptake had a negative relationship with blood glucose levels in this study (12,13). In a previous study, experimentally induced hyperglycemia resulted in lower brain uptake and higher FDG uptake in the blood compared to the controls in rats (2). In another study, Lindholm et al. showed a statistically significant correlation between the blood glucose values and blood FDG uptake (14). In contrast, Kuruva et al. found no significant differences between these variables (15). In this study, there was no association between glucose level and mediastinal blood FDG uptake. In a review, the authors concluded that effect of glycemia on the mediastinal blood pool appears to be insignificant (16).

Myocardial metabolism is very complex. Normally, the myocardium utilizes free fatty acid, glucose and lactate. In addition to the fasting period and fasting blood sugar, many factors such as age, insulin, glucagon, catecholamine and thyroxin levels, and nicotinic acid may be related to the myocardial FDG uptake (17-19). Some studies have shown

that the heart's FDG uptake has no relationship with the blood glucose level (20) but others have shown a negative relationship between these parameters (21). In this study, there was no association between the blood glucose level and myocardial FDG uptake. Prospective studies with a large number of patients and evaluating other factors affecting myocardial FDG uptake are needed to assess these findings. The effect of glycemia on the liver FDG uptake is inconclusive. Although most studies demonstrated a significant positive association between liver uptake and blood glucose level (12,22), only a few studies have shown a non-significant association between glycemia and liver FDG uptake (14). In a review, the authors concluded that liver FDG uptake is affected by the glycemic levels, but this effect is too small for clinical relevance (16). Liver SUVmean demonstrated a positive correlation with blood glucose levels in this study ($p < 0.05$). Liver FDG uptake is important

because it is the reference organ for calculation of the tumor-to-background ratio and assessment of treatment response according to the PET Response Criteria in Solid Tumors (PERCIST). In a study, Sprinz et al. concluded that the lung is the organ least affected by some variables including glycemia and may serve as an alternative background tissue to the liver (8). Many studies including this study have shown that there was no association between blood glucose level and lung FDG uptake (11,14). Additionally, in accordance with the literature, there was no correlation between glycemia and bone marrow, spleen and pancreas FDG uptake in this study (11,14,16).

Increased insulin levels secondary to elevated blood glucose increases the translocation of GLUT4 transporter, causing rapid and efficient shunting of ^{18}F -FDG to the organs with a high density of insulin receptors such as skeletal muscles, resulting in altered tracer biodistribution and suboptimal image quality (23). Lindholm et al. showed that the muscle accumulated more FDG after glucose loading than in the fasting state (14). Contrary to these studies (22), many studies including this one showed increased muscle FDG uptake in the patients with a high glucose level (11). This study has some limitations. Firstly, this study includes a relatively small number of cases. Because the study was designed as a retrospective study, many factors such as body mass index and diabetes status that may affect the ^{18}F -FDG uptake of tissues could not be evaluated. Additionally, only acute hyperglycemia cases could be evaluated in this study. FDG uptake of normal tissues is affected mostly by acute hyperglycemia compared to chronic hyperglycemia (24).

In conclusion, the effect of hyperglycemia during ^{18}F -FDG PET/CT imaging on normal tissues is variable. Elevated glucose levels affect FDG uptake in the normal brain, liver and skeletal muscles. Prospective studies with a large number of patients and evaluating both acute and chronic hyperglycemia are needed to assess these findings.

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