Original Article

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Physiological Distribution of ^{18}F-FDG in the Spinal Cord of Disease-Free Subjects

Hastalıksız Bireylerde Spinal Kordda Fizyolojik ^{18}F-FDG Dağılımı

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Abstract

Objectives: ^{18}Fluorine-fluorodeoxyglucose (^{18}F-FDG) uptake in the spinal cord is not unusual and may mimic metastatic disease. The physiological characterization and variability of spinal cord ^{18}F-FDG metabolism provide valuable information, especially in patients with suspected malignancies. We aimed to investigate the physiological ^{18}F-FDG uptake pattern within the spinal cord and its associations in a normal population.

Methods: We retrospectively analyzed ^{18}F-FDG positron emission tomography/computed tomography images of 140 adult patients who were confirmed to be disease-free over a one-year follow-up period. The maximal and mean standard uptake values (SUV_{max}, SUV_{mean}) were measured at each mid-vertebral level from C1 to L5, and normalized to liver and blood pool uptake. Correlations between ^{18}F-FDG uptake and patient demographics, clinical parameters, and environmental temperature were evaluated.

Results: ^{18}F-FDG uptake demonstrated a decreasing trend from the cervical to lumbar vertebrae, with a notable increase at the lower thoracic levels (T11-T12). There was a significant negative correlation between ^{18}F-FDG uptake and age ($p<0.001$), fasting glucose level ($p=0.016$), and diabetic status ($p=0.003$). No significant association was found between spinal cord ^{18}F-FDG uptake and gender, weight, height, body mass index, ^{18}F-FDG dose, or environmental temperature.

Conclusion: Normal distribution of ^{18}F-FDG in the spinal cord of disease-free individuals decreases from cervical to lumbar levels, although it notably increases at the lower thoracic and mid-lower cervical levels. Uptake significantly decreases with age, with a higher fasting blood glucose level, and in diabetic patients.

Keywords: Spinal cord, ^{18}Fluorine-fluorodeoxyglucose,, positron emission tomography/computed tomography, physiological uptake

Öz

Amaç: Spinal kordda ^{18}Flor-florodeoksiglukoz (^{18}F-FDG) tutulumu nadir değildir ve metastatik hastalığı taklit edebilir. Spinal kord ^{18}F-FDG metabolizmasının fizyolojik karakterizasyonu ve değişkenliği, özellikle malignite şüphesi olan hastalarda değerli bilgiler sağlar. Bu çalışmada, normal popülasyonda spinal korddaki fizyolojik ^{18}F-FDG tutulum paternini ve ilişkilerini araştırmayı amaçladık.

Yöntem: Bir yıllık takip süresi boyunca hastalıksız olduğu teyit edilen 140 yetişkin hastanın ^{18}F-FDG pozitron emisyon tomografisi/bilgisayarlı tomografi görüntüleri retrospektif olarak incelendi. C1'den L5'e kadar her orta-vertebral seviyede spinal kanalın maksimum ve ortalama standart

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tutulum değerleri (SUV_{maks}, SUV_{ort}) ölçüldü ve karaciğer ve kan havuzu tutulumu ile normalize edildi. ^{18}F-FDG tutulum yoğunluğu ile hastaların demografik özellikleri, klinik parametreleri ve çevre sıcaklığı arasındaki korelasyonlar araştırıldı.

Bulgular: Spinal korddaki ^{18}F-FDG tutulumu servikal vertebralardan lomber vertebralara doğru azalan bir patern göstermiş olup alt torasik (T11-T12) seviyelerde anlamlı bir artış izlenmiştir. ^{18}F-FDG tutulumu ile yaş ($p<0,001$), açlık glukoz düzeyi ($p=0,016$) ve diyabetik durum ($p=0,003$) arasında anlamlı bir negatif korelasyon bulunmuştur. Spinal kord ^{18}F-FDG tutulumu ile cinsiyet, kilo, boy, vücut kitle indeksi, ^{18}F-FDG dozu veya çevre sıcaklığı arasında ise anlamlı bir ilişki saptanmamıştır.

Sonuç: Hastalıksız bireylerde spinal kordda ^{18}F-FDG dağılımı servikalden lumbar seviyelere doğru azalmakta olup alt torasik ve orta-alt servikal seviyelerde belirgin artış göstermektedir. ^{18}F-FDG tutulumu artan yaşla, açlık kan şekeri seviyesinin yükselmesiyle ve diyabetik hastalarda önemli ölçüde azalmaktadır.

Anahtar kelimeler: Spinal kord, ^{18}Flor-florodeoksiglukoz,, pozitron emisyon tomografisi/bilgisayarlı tomografi, fizyolojik tutulum

Introduction

^{18}Fluorine-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT) imaging is increasingly being used in the initial diagnosis, staging, restaging, and monitoring therapy response in oncological patients. The physiological distribution of ^{18}F-FDG has been welldefined; it has high uptake in the heart, liver and brain, eliminates in urine, and concentrates in the gastrointestinal tract with varying degrees. ^{18}F-FDG uptake in the spinal cord is not unusual and may be either physiological or indicative of underlying diseases such as metastatic involvement, vascular, infectious, or inflammatory diseases (1). Spinal metastases constitute approximately 8.5% of all the central nervous system metastases, with lung and breast cancer being the most common primaries (2). Normal variants of physiological uptake in the spinal cord can cause misdiagnosis and unnecessary treatments in oncologic patients. Hence, it is crucial to understand the physiologic distribution of ^{18}F-FDG in the spinal cord for a correct interpretation of PET imaging.

Several studies examined the physiological distribution of ^{18}F-FDG within the spinal cord of adult cancer patients with non-central nervous system malignancies (1,3,4,5,6,7,8), while two studies evaluated the physiological metabolism of the spinal cord in oncologic pediatric patients (9,10). However, these studies have confounding factors such as chemotherapy, radiation therapy, or surgery, that might affect ^{18}F-FDG uptake in the spinal cord due to radiation myelopathy (11,12). To date, only two studies with small sample sizes (n=16, n=30) reported physiologic uptake of ^{18}F-FDG within the spinal cord in disease-free patients (13,14). The aim of this study is to evaluate the physiological ^{18}F-FDG distribution within the spinal cord in disease-free subjects, and assess the influence of gender, age, body weight, body mass index (BMI), diabetes and environmental temperature on spinal cord ^{18}F-FDG uptake in a larger cohort population.

Materials and Methods

Study Design and Patient Selection

We retrospectively evaluated ^{18}F-FDG PET/CT images of adult patients who were referred to our clinic for evaluating suspected malignancy, or characterization of solitary pulmonary nodules over a 24-month period from June 2021 to June 2023. Only 140 patients who were proven to be disease-free during a one-year follow-up were included in the study. Patients with abnormal ^{18}F-FDG PET/CT findings suggestive of malignant disease, a history of former malignancies, chemotherapy, inflammatory or degenerative vertebral diseases affecting spinal cord, and previous spinal operations were excluded from participating in the study. Additionally, patients whose fasting blood glucose levels were higher than 126 mg/dL were excluded, in accordance with the European Association of Nuclear Medicine procedural guidelines for research studies (15). Medical parameters including gender, age, weight, height, BMI, fasting glucose level, diabetes status, and ^{18}F-FDG dose were recorded. Daily local average temperature values were obtained from the national meteorology archives. This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. Approval was obtained from the Marmara University Faculty of Medicine Clinical Research Ethics Committee (number: 09.2021.1437, date: 03.12.2021) and informed consent was obtained from each participant.

^{18}F-FDG PET/CT protocol

^{18}F-FDG PET/CT images were acquired after a 6-hour fast and approximately 1 hour after intravenous injection of ^{18}F-FDG using a dedicated combined scanner (GE Discovery ST; GE Healthcare, Milwaukee, WI). All patients had a blood sugar level of less than or equal to 126 mg/dL before ^{18}F-FDG injection. First, a multi-slice CT scan was performed with a 16-slice multidetector scanner (parameters: 80 mA; 140kV; table speed: 27 mm/rotation; and slice thickness: 3 mm) from the top of the head through the feet in the

supine position in a shallow breathing patient. A routine whole-body PET scan was conducted in 3D mode, with an acquisition time of 3 minutes per bed position, covering the same area as the CT scan. PET data were reconstructed using an iterative processing algorithm, and the acquisition data transferred to a workstation (Advantage Windows Server 4.5; GE Healthcare) for manual segmentation and interpretation.

Image Analysis

All ^{18}F-FDG PET/CT images were evaluated by two experienced nuclear medicine physicians.

The maximal and mean standard uptake values (SUV_{max}; SUV_{mean}) of the spinal cord at each mid-vertebral level from C1 to L5 were recorded with a standard region of interest (ROI) size. The ROIs for each spinal cord measurement were manually drawn while avoiding the margins of vertebrae (Figure 1). For internal normalization, a reference ROI was placed over the liver, on the 6th hepatic segment, and over the blood pool, particularly on the right atrium, to calculate the normalized SUV_{max} ($nSUV_{max}$) and the normalized SUV_{mean} ($nSUV_{mean}$) values.

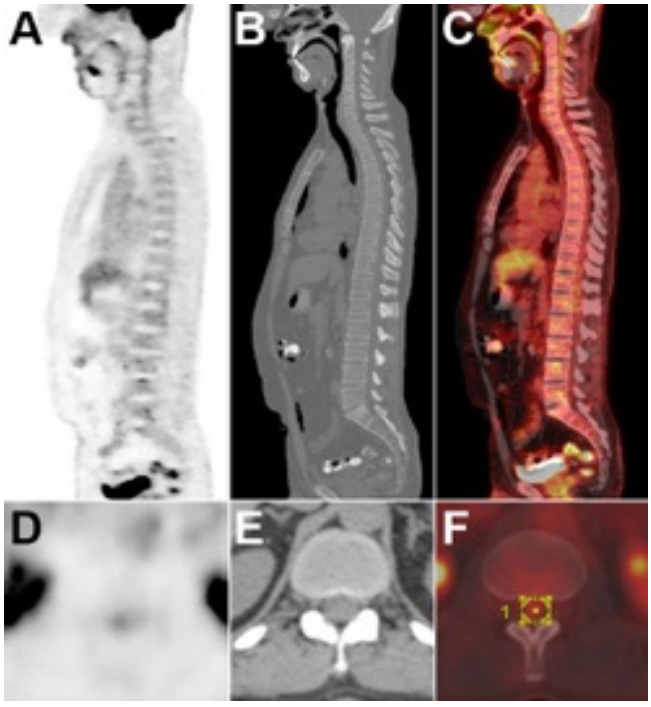

Figure 1. Example of region-of-interest (ROI) delineation for ^{18}F-FDG uptake in the spinal cord. ROIs were manually drawn on fused PET/CT images at the mid-height of each vertebral body level from C1 to L5, avoiding the vertebral margins. (A; sagittal PET image, B; CT image, C; fused PET/CT image, D-E; axial PET, CT, and fused PET/CT images)

PET/CT: Positron emission tomography/computed tomography, ^{18}F-FDG: ^{18}Fluorine-fluorodeoxyglucose

Statistical Analysis

Descriptive statistics were used to present the characteristics of the study population. Continuous data were reported as means ± standard deviations or median, (range), while categorical variables were expressed as frequencies (percentage). A preliminary Kolmogorov-Smirnov test was used to assess the normality of variables. Means were compared with Student's t-test. The correlations of SUV with age, weight, ^{18}F-FDG dose, and temperature were tested with Spearman's correlation analysis. Pearson's correlation analysis was used to determine the relationship between glucose level, height, BMI, and the ^{18}F-FDG uptake of each vertebral level. The pattern of physiological spinal cord, ^{18}F-FDG, distribution was determined by drawing a graph based on the mean $nSUV_{max}$/$nSUV_{mean}$ of each vertebral level. Data were analyzed using IBM SPSS® software version 29.0. Results with two-sided $p<0.05$ were considered statistically significant.

Results

Patient Characteristics

One hundred forty patients (72 men, 68 women) who met the inclusion criteria and were enrolled in the study. The mean age of the patients was 55±16 (men 54.9±16, women 55.2±16.2) years, while the median age was 53.5. Population characteristics are summarized in Table 1.

SUV Measurements

The highest SUV_{max} value was noted at the C1 level (range 1.3-3.1, mean 2.1), while the lowest SUV_{max} value was observed at the L5 level (range 0.5-2.4, mean 1.1). Physiologic ^{18}F-FDG uptake showed a decreasing pattern in the spinal cord from cervical to lumbar vertebrae with a significant increase at the lower thoracic (T11-T12) levels and a relatively insignificant increase at mid-cervical (C4) level. It is notable that the SUV_{max} and SUV_{mean} values, as well as $nSUV_{max}$ and $nSUV_{mean}$ values, were highly correlated ($p<0.000$). The mean SUV_{max} of the spinal cord at the C1 and T12 levellevels was 2.1 and 1.8, respectively. Normal distribution of maximal spinal cord SUV measurements is presented in Figure 2.

Factors affecting ^{18}F-FDG uptake in the spinal cord

There was a statistically significant association between spinal cord ^{18}F-FDG uptake intensity and the presence or absence of diabetes ($p=0.003$). Also, spinal cord ^{18}F-FDG uptake had a negative correlation with age and fasting glucose level ($r=-0.37$, $p<0.001$ and $r=-0.20$, $p=0.016$, respectively, Figure 3). However, no significant association was found between spinal cord ^{18}F-FDG uptake intensity and

Table 1. Patient characteristics			
	n (%)	**n (%)**	**p-value**
Gender	72 (51.4%) men	68 (48.6%) women	0.27[a]
Diabetic status	21 (15%) diabetic	119 (85%) non-diabetic	**0.003**[a]
	Mean	**Range**	
Age	55±16 y	18-88 y	**<0.001**[b]
Weight	73.4±14.6 kg	41-120 kg	0.29[b]
Height	166.6±8.9 cm	140-190 cm	0.51[c]
BMI	26.5±5.2	16.5-44	0.44[c]
Fasting blood glucose level	90±14 mg/dL	60-125 mg/dL	**0.016**[b]
F-18 FDG dose	6±0.5 mCi (222±18.5 MBq)	4.6-7.6 mCi (170-281 MBq)	0.70[b]
Environmental temperature	16±7 °C	0-28.7 °C	0.27[b]

[a]Student t-test, [b]Pearson correlation test, [c]Spearman correlation test, BMI: Body mass index, FDG: 18Fluorine-fluorodeoxyglucose

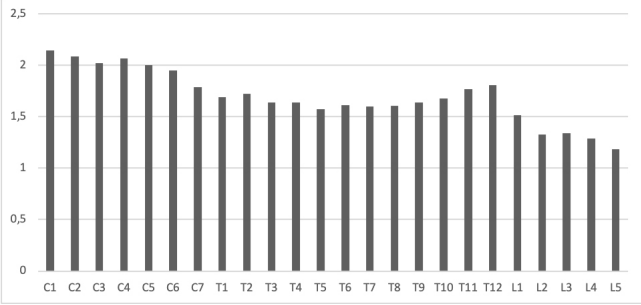

Figure 2. Distribution of ^{18}F-FDG uptake in the spinal cord at each mid-vertebral level

^{18}F-FDG: ^{18}Fluorine-fluorodeoxyglucose

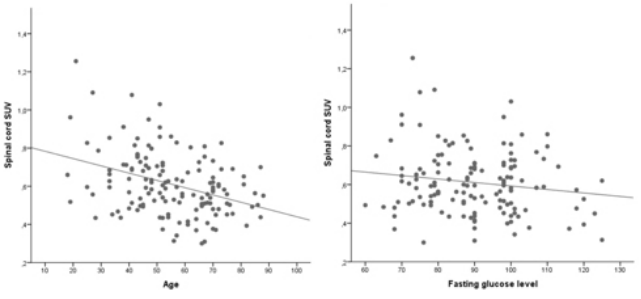

Figure 3. Correlation of mean spinal cord nSUV at the T12 level with age and fasting glucose levels

nSUV: Normalized standardized uptake value

gender (p=0.27), patient weight (p=0.29), height (p=0.51), BMI (p=0.44), ^{18}F-FDG dose (p=0.70), or environmental temperature (p=0.27). Figures 4 and 5 demonstrate that there is a decrease in ^{18}F-FDG uptake in the spinal cord in patients with diabetes and with increasing age, respectively.

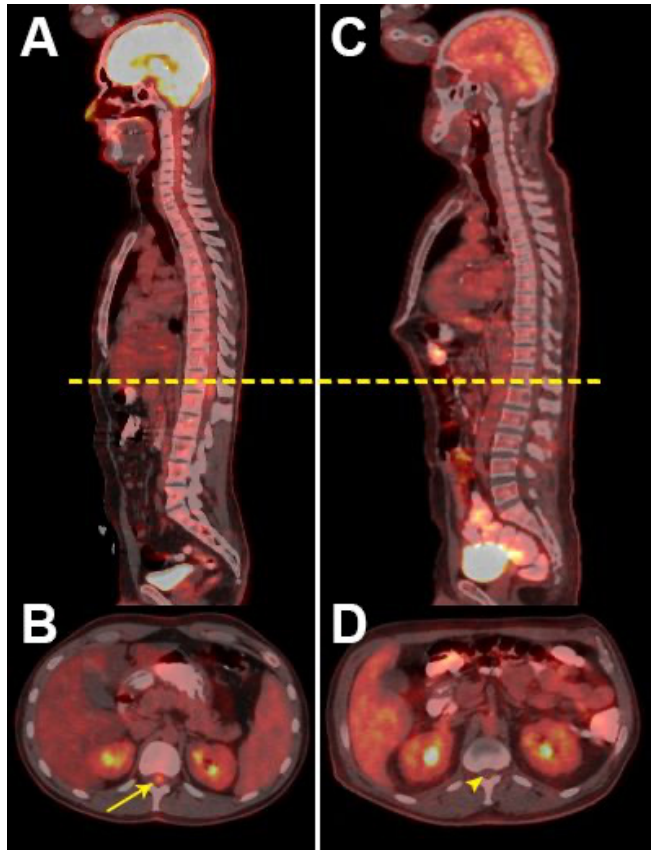

Figure 4. Demonstration of decreased ^{18}F-FDG uptake in diabetic patients. (A) Sagittal and (B) axial fused PET/CT images of a 41-year-old man, who does not have diabetes and and has a fasting glucose level of 79 mg/dL, showing higher spinal cord ^{18}F-FDG uptake (arrow) compared to (C) sagittal and (D) axial fused PET/CT images of a 50-year-old man, who has diabetes and a fasting glucose level of 125 mg/dL (arrowhead)

PET/CT: Positron emission tomography/computed tomography, ^{18}F-FDG: ^{18}Fluorine-fluorodeoxyglucose

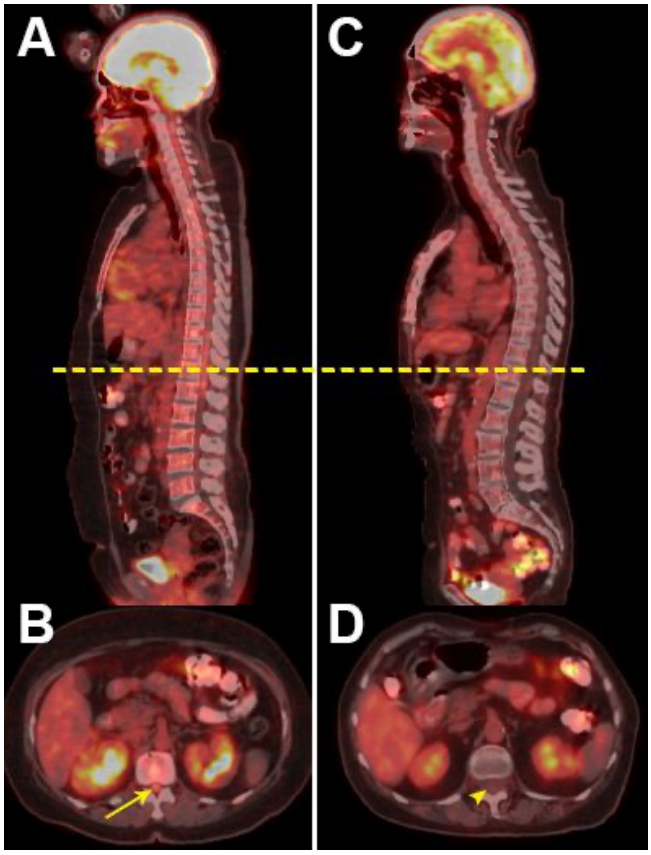

Figure 5. Demonstration of decreased ^{18}F-FDG uptake with age in non-diabetic patients. (A) Sagittal and (B) axial fused PET/CT images of a 31-year-old woman showing higher spinal cord ^{18}F-FDG uptake (arrow) compared to (C) sagittal and (D) axial fused PET/CT images of a 75-year-old woman (arrowhead)

PET/CT: Positron emission tomography/computed tomography, ^{18}F-FDG: ^{18}Fluorine-fluorodeoxyglucose

Discussion

Our results confirm that spinal cord ^{18}F-FDG uptake significantly correlates with patients' age, fasting blood glucose level and diabetic status. No significant association was found between SUV and gender, patient weight, height, BMI, ^{18}F-FDG dose, or environmental temperature. This study also shows the physiological distribution of ^{18}F-FDG uptake within the spinal cord, which is more evident in the cervical and lower thoracic levels. The main difference in our study lies in the study population, which is therapy-naive and proven to be disease-free with the largest sample size reported in the literature.

Several studies reported spinal cord ^{18}F-FDG distribution with a variety of investigation methods. Only two studies calculated SUV_{max} of all spinal segments and reported a decreasing pattern from cervical to lumbar levels with an increase at the lower thoracic and mid-lower cervical levels, which complies with our results (1,14). This pattern is attributed by the authors to cervical and lumbar enlargement and the increased amount of gray matter in children and adults (1,6,9). Another aspect of our study was to evaluate the consistency of SUV calculated within the spinal cord and those normalized to liver or blood pool. The physiological distribution of SUV_{max} and SUV_{mean} in the spinal cord correlated well with the distribution of $nSUV_{max}$ and $nSUV_{mean}$.

Most of the studies reported in the literature were carried out in patients with a history of cancer and radiation therapy. However, white matter necrosis, demyelination, and malacia are typical features of radiation damage to the spinal cord, which may result in decreased ^{18}F-FDG uptake (16). In addition, radiation myelopathy is associated with increased ^{18}F-FDG uptake in the irradiated spinal cord (11,12). Although some studies excluded patients who had previously received radiation therapy, the studies did not consider the impact of chemotherapy, which could also interrupt the blood-spinal cord barrier, resulting in edema, demyelination, and finally necrosis and atrophy of the spinal cord (17).

Two pediatric studies reported a significant increase in SUV within the spinal cord with increasing age (9,10). In adult patients, most studies did not find any correlation between spinal cord ^{18}F-FDG uptake and age (1,3,5,14,18). Contrary to these studies, Kamoto et al. (19) and Tan et al. (20) reported a negative association between metabolic activity of the spinal cord and age in oncologic patients. Our study is the first to determine a negative correlation between age and spinal cord metabolic activity in a healthy adult population. Although neural plasticity and volumetric growth of the spinal cord during childhood development could be responsible for the positive correlation between age and spinal cord activity, age-related decreases in SUV in adult patients may be a reflection of age-associated structural atrophy, reduced nerve conduction velocity, and reduced motor activity (21).

Greenspan et al. (7) reported a statistically significant association between distal spinal cord uptake and lower blood glucose levels; however, there was no significant association between patients' diabetic status and any other variable. In 2022, Tan et al. (20) reported that intense ^{18}F-FDG uptake in the distal spinal cord was more common in patients without diabetes and with lower blood glucose levels. Contrarily, the studies conducted by Nakamoto et al. (18) and Patel et al. (5) did not find a correlation between the plasma glucose level and the cervical spinal cord ^{18}F-FDG uptake. In our study, mean spinal cord SUV

and nSUV values were lower in diabetic patients, who also exhibited higher glucose levels. Previous studies reported lower cerebral ^{18}F-FDG uptake in patients with diabetes (22). Although the pathogenesis is not fully understood, insulin-induced upregulation of hepatic glucokinase results in hepatocellular glucose uptake and increased glucose flux to the central nervous system. While hyperglycemia is reported to have a greater impact on ^{18}F-FDG uptake in the central nervous system compared to the liver (23), the reduced SUV and nSUV in our study group may be explained by poorly controlled hyperglycemia in diabetes, leading to competitive inhibition of ^{18}F-FDG uptake in normal tissues.

In this study, no association was found between patients' weight, height, or BMI and spinal cord metabolism. A few studies reported a positive correlation between body weight and spinal cord ^{18}F-FDG uptake (6,10). Since ^{18}F-FDG distribution is very low in adipose tissue, higher SUV is expected in overweight patients. This vague result could be mitigated by applying SUV correction for lean body mass or body surface area.

With regard to seasonal variation, Amin et al. (3) reported increased cord ^{18}F-FDG uptake in winter, which is based on the hypothesis that activation of the sympathetico-adrenal system leads glucose flux to the central nervous system. However, similar to the results reported by other investigators, we did not find a relation between environmental temperature and spinal cord ^{18}F-FDG uptake (4,10,14).

An association between gender and cord uptake has been investigated by many authors. Greenspan et al. (7) and Taralli et al. (10) reported a positive correlation with female sex. This can be explained by the higher metabolism of the lumbosacral tract secondary to women's reproductive system innervation. However, sex difference was not reported in most other studies, which are similar to our results (3,5,14,18,20).

The limitations of this study include its retrospective design. Also, the time interval between ^{18}F-FDG injection and imaging was not taken into account in correlation analyses. Nevertheless, the strong points of our study are the SUV measurement method, which includes each mid-vertebral spinal level, and the inclusion of a specific disease-free patient group.

Conclusion

In normal subjects, physiological ^{18}F-FDG uptake in the spinal cord decreases from cervical to lumbar levels, although there is an increase noted at the lower thoracic and mid-lower cervical regions. The present study provides evidence that spinal cord ^{18}F-FDG uptake significantly decreases with increasing age, blood glucose level, and diabetes status in patients. Even though our study included the largest number of normal adult participants to date, the conflicting results with other studies reported in the literature warrant further research with larger sample sizes to obtain more conclusive results.

Ethics

Ethics Committee Approval: Approval was obtained from the Marmara University Faculty of Medicine Clinical Research Ethics Committee (number: 09.2021.1437, date: 03.12.2021).

Informed Consent: Informed consent was obtained from each participant.

Footnotes

Authorship Contributions

Surgical and Medical Practices: S.K., S.Ö., Concept: S.Ö., Design: S.Ö., Data Collection or Processing: S.K., Analysis or Interpretation: S.K., Literature Search: S.K., Writing: S.K.

Conflict of Interest: No conflict of interest was declared by the authors.

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