Evaluation of physiological FDG uptake in the skeleton in adults: Is it uniformly distributed?†

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A B S T R A C T

Aim: The aim of this study was to study whether FDG was uniformly distributed throughout the skeleton and whether age and gender affected this biodistribution.

Material and Methods: A total of 158 patients were included in this retrospective study. None of the patients had received prior treatment that had affected the bone marrow and patients with bone metastases, trauma, benign and/or malignant hematologic disorders were excluded from the study. The SUVmax from the 24 different locations in the skeleton was obtained and all the values were compared with each other.

Results: FDG uptake in the skeleton was not uniform in both sexes. While the highest FDG uptake was seen in the L3 vertebra, the lowest glucose metabolism was observed in the diaphysis of the femur. Concerning the vertebral column, FDG uptakes were also non-uniform and the SUVmax gradually increased from the cervix to the lumbar spine. The mean skeletal SUVmax was decreased in accordance with age in both genders.

Conclusion: FDG was not uniformly distributed throughout the skeleton in both sexes. It had a tendency to increase from the appendicular to axial skeleton and from cervical to lumbar spine in the vertebral column that may be related with the normal distribution of the red bone marrow. Additionally, the glycolytic metabolism of the whole skeleton was gradually decreased in accordance with the age in both sexes.

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Evaluación de la captación fisiológica de FDG en el esqueleto en adultos: ¿Está uniformemente distribuida?

R E S U M E N

Objetivo: El objetivo de este estudio fue investigar si la FDG se distribuye uniformemente por todo el esqueleto y si la edad y el género afectan la biodistribución.

Material y Métodos: Un total de 158 pacientes fueron incluidos en este estudio retrospectivo. Ningún paciente había recibido tratamiento previo que afectara a la médula ósea y los pacientes con metástasis óseas, trauma, trastornos hematológicos benignos y/o malignos fueron excluidos del estudio. Se obtuvieron las SUVmax de las 24 ubicaciones diferentes en el esqueleto y todos los valores se compararon entre sí.

Resultados: La captación de FDG en el esqueleto no fue uniforme en ambos sexos. Mientras que la captación de FDG más alta se observó en la vértebra L3, el metabolismo de la glucosa más bajo se observó en la diáfisis de los fémures. Con respecto a la columna vertebral, la FDG captación tampoco fue uniforme y la SUVmax aumentó gradualmente desde la columna cervical a la columna lumbar. La SUVmax media esquelética se redujo según la edad en ambos sexos.

Conclusión: La FDG no se distribuyó de manera uniforme en todo el esqueleto en ambos sexos. Tuvo una tendencia a aumentar desde las extremidades al esqueleto axial y desde la columna cervical a la columna lumbar y que puede estar relacionado con la distribución normal de la médula ósea roja. Además, el metabolismo glicolítico de todo el esqueleto se redujo gradualmente a medida que avanzaba la edad en ambos sexos.

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Introduction

Fluorodeoxiglucose (FDG), as a glucose analog, is the most commonly used PET radiopharmaceutical in current nuclear oncology practice. Although it is transported into the cell via the same mechanisms as glucose, it is not further metabolized and entrapped in...
proportion to the rate of glucose metabolism. FDG is not only used by the tumor cells. Heart, brain and urinary tract are the most apparent sites that physiological FDG activity is readily seen. Apart from these, some of the structures in the body, such as bone marrow, may show variable FDG uptake.\(^2\) In adult patients, normally no FDG uptake is identified in the bone. However physiological linear uptake in physes and apophyses may be seen in skeletally immature pediatric patients.\(^1\) FDG uptake in the bone marrow is generally modest with an SUV of less than 3 and bone marrow activity that is more intense than liver activity is considered as abnormal.\(^1\)\(^,\)\(^3\) However, as mentioned above bone marrow uptake is variable and such generalizations may affect the sensitivity and specificity of the examination. The aim of the current study was to investigate the differential physiological FDG biodistribution in different sites of the skeleton.

**Material and methods**

**Patient population**

A total of 158 cancer patients (100 female, 58 male) referred for initial staging with FDG PET/CT were included in this retrospective study. Several therapeutic interventions (e.g., chemotherapy, radiotherapy, synthetic hematopoietic growth factors, etc.) and pathologic states (e.g., benign and/or malignant hematologic disorders, infection, etc.) were known to affect the physiological bone marrow FDG uptake.\(^4\)\(^,\)\(^5\) In our study we screened patients’ hospital records (e.g., previous laboratory tests, radiological examinations, treatment records) to exclude these causes. The patients with history of bone metastases, trauma, benign and/or malignant hematologic disorders were excluded from the study. All the patients had follow-up FDG PET/CT performed within 3 months after the initial scan. Subjects with bone metastases in this follow-up PET/CT were also excluded.

**Imaging method**

Although oral hydration with glucose-free water was allowed, all patients had fasted for at least 6 h before image acquisition. None of them were diabetic and the blood glucose levels that were checked before FDG administration were below 200 mg/dL. After I.V. injection of 370 MBq (10 mCi) of FDG, all patients were asked to rest in a quiet room for 60 min. According to our departmental protocol, we use oral but not I.V. contrast agent. Image acquisition was performed using an integrated PET/CT system (Discovery-16 LS, GE Healthcare). PET images were acquired from mid-skull to mid-thigh in 3D-mode and reconstructed in transverse, coronal, and sagittal planes. A low-dose CT scan was performed for attenuation correction and anatomic orientation. After the acquisition, data were transferred to a workstation (Advantage Windows Workstation 4.5, GE Healthcare) for processing and interpretation.

**Image analysis**

SUVmax of the 24 different locations in the skeleton [the diaphysis and proximal metaphysis of the bilateral humerus and femur, 10th rib, sternum (manubrium and corpus), vertebral column (C3, C5, T3, T7, L1, L3) and bilateral pelvic bones (sacrum and bilateral anterior and posterior parts of the iliac bones and acetabulum)] were obtained by drawing volume of interests (VOI), (irregular, voxel) in each region (Fig. 1). Degenerative changes were not included in the VOI. All the values were summed, averaged and compared with each other. The mean skeletal SUVmax for each subject was calculated by averaging the SUVmax values of the aforementioned 24 locations.

**Statistical analysis**

Statistical analysis was performed by GraphPad InStat Version 3.00 (GraphPad Software Inc, San Diego, California, USA). Based on analyzed data, Kruskal–Wallis test (nonparametric ANOVA), the Mann–Whitney U-test, and linear regression analysis were used. A p value less than 0.05 was considered to be statistically significant.

**Results**

In a total of 158 cancer patients (female/male, 100/58), (55 breast cancer, 43 colorectal cancer, 37 lung cancer, 5 gastric cancer, 12 larynx cancer, 6 testicular cancer) the mean age (female: 57.6 ± 13.8 years, male: 59.3 ± 14.4 years, p > 0.05) and the mean SUVmax of sum of 24 different locations in the skeleton (female: 2.1 ± 0.4, male: 2.0 ± 0.3, p > 0.05) were similar regardless of gender.
When taken together for both sexes, FDG uptake in the skeleton was not uniform ($p < 0.05$). While the highest FDG uptake was seen in L3 vertebra (mean SUVmax: $2.9 \pm 0.7$), the least glucose metabolism was observed in the diaphysis of the lower extremities (mean SUVmax: $1.4 \pm 0.3$). The SUVmax of the bilateral proximal metaphyses of the humeri and femora was significantly higher than the neighboring diaphysis ($p < 0.05$). The SUVmax of the manubrium of the sternum was significantly higher than the corpus ($p < 0.05$). For pelvic bones, while the highest FDG uptakes were detected in sacrum (mean SUVmax: $2.6 \pm 0.7$), the least FDG uptakes were seen in anterior iliac bones (SUVmax: $1.8 \pm 0.4$), ($p < 0.05$). Concerning the vertebral column FDG uptakes were also non-uniform and the SUVmax gradually increases from cervical to lumbar spine (C3-mean SUVmax: $2.2 \pm 0.4$, L3-mean SUVmax: $2.9 \pm 0.7$), ($p < 0.05$) (Fig. 2). The mean skeletal SUVmax was decreased by the age in both sexes ($r: -0.25, p < 0.05$) (Fig. 3).

Discussion

The bone marrow is found within the central cavities of axial and long bones. It constitutes approximately 5% of the total body weight in adults. The two major components of the bone marrow are red and yellow marrow.

The present study showed that FDG uptake in the skeleton was not uniform. It gradually increased from appendicular to axial skeleton. These findings are compatible with the normal distribution of red marrow. In healthy adults, red marrow predominates in the axial skeleton and proximal ends of the humeri and femurs. The different FDG uptake patterns in these two types of bone marrow may be explained by their relative cell composition. Although majority of the yellow marrow is filled by fat cells (~95%), hematopoietic cells are the primary component of the red marrow (~60%).

Our study also demonstrated that bone marrow metabolism was gradually decreased by the age. Similar to our results, Inoue et al. and Blebea et al. also found a negative correlation between age and bone marrow FDG uptake. This may be explained by the physiological age-related transformation from red to yellow marrow. At birth, the bone marrow is filled by hematopoietic red marrow, then it is gradually replaced by fatty yellow marrow with an approximately 10% decrease in cellularity for each decade of life. The transformation from red to yellow marrow
begins in the appendicular skeleton and progresses to the axial skeleton.\textsuperscript{3,11,15} In the present study we also observed that the mean SUV\textsubscript{max} of the bilateral proximal metaphyses of the humeri and femora was higher than the neighboring diaphysis. This difference can also be attributed to the normal age-related marrow conversion. In long bones, marrow conversion occurs first in the diaphysis, then in the distal metaphyses, and finally in the proximal metaphyses.\textsuperscript{9,10} Although the adult pattern of marrow distribution – that is the red marrow is located primarily in the axial skeleton, sternum, ribs, and proximal femora and humeri – is generally reached by the age of 25, marrow conversion also proceeds in adulthood but with a slower rate.\textsuperscript{9,11,15}

To our knowledge, the physiological FDG uptake in the vertebral column has not been evaluated yet. Our results revealed a gradual increase in SUV\textsubscript{max} from cervical to lumbar spine in the vertebral column. In the literature, there are morphological studies with MRI about the marrow composition of the vertebral column.\textsuperscript{16} However, they could not document a significant difference in terms of marrow distribution and signal intensity patterns in the same individual.

**Limitations**

In our study all the patients with apparent bone metastasis were excluded from the study. Although we tried to eliminate the probability of bone metastasis by performing a follow-up PET/CT within 3 months after the initial scan we did not know whether or not they had bone metastasis under PET resolution limits at the time of PET/CT imaging. Additionally, although we had included 158 patients, we did not have adequate sample size from all age groups to perform a subgroup analysis. Most of our patients were older than 50 years of age.

**Conclusion**

In conclusion, FDG was not uniformly distributed throughout the skeleton in both sexes. It had a tendency to increase from appendicular to axial skeleton and from cervical to lumbar spine in vertebral column which may be related with the normal distribution of the red marrow. Additionally, the glycolytic metabolism of whole skeleton was gradually decreased by the age in both genders. The awareness of this physiological heterogenous FDG distribution in the skeleton is important for reliably identifying marrow involvement in FDG PET/CT studies.

**Conflicts of interest**

All the authors state that there were no conflicts of interest when the manuscript was written.

**References**