Brown adipose tissue: a factor to consider in symmetrical tracer uptake in the neck and upper chest region

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Revised: 28 May 2002 / Published online: 8 August 2002

Abstract. Increased symmetrical fluorine-18 fluorodeoxyglucose (FDG) uptake in the cervical and thoracic spine region is well known and has been attributed to muscular uptake. The purpose of this study was to re-evaluate this FDG uptake pattern by means of co-registered positron emission tomography (PET) and computed tomography (CT) imaging, which allowed exact localisation of this uptake. Between April and November 2001, 638 consecutive patients referred for PET/CT were imaged on an in-line PET/CT system (GEMS). This system combines an advanced GE PET scanner and a multirow-detector computer tomograph (Lightspeed, GEMS). The examination included PET with FDG and one CT acquisition with 80 mA. For CT, the following parameters were used: 140 kV, 80 mA, reconstructed slice thickness 5 mm, scan length 867 mm, AT 22.5 s. CT data were used for attenuation correction as well as image co-registration. Image analysis was performed on an Entegra work-station (ELGEMS). All patients with symmetrical uptake within the neck, thorax and shoulder regions were selected and the exact localisation of uptake determined (muscle, bone, fatty tissue or articulation). In 17 of the 638 patients (2.5%), increased, symmetrical FDG uptake in the shoulder region in a typical pattern was found. If extensive, this pattern included FDG activity comparable to brain activity in the lower cervical spine, the shoulder region and the upper thoracic spine in the costovertebral region. A less extensive pattern only involved intermediate FDG uptake in the lower cervical spine and shoulder region or in the shoulder region alone. In seven female patients (average 32.3 years), the extensive uptake pattern was seen. The average body mass index (BMI) was 19.0 (range 16.8–23.4). In the other ten patients (two male, eight female, average age 37.1 years), the average BMI was 22.7 (18.7–27.7). In all patients, the soft tissue uptake was clearly localised within the fatty tissue of the shoulders as demonstrated by PET/CT co-registration. The uptake in the region of the thoracic spine was localised in the region of the costovertebral joints. Symmetrical FDG uptake in the shoulder, neck and thoracic spine region is probably related to uptake in adipose tissue, especially in underweight patients. Hypothetically, this FDG uptake could represent activated brown adipose tissue during increased sympathetic nerve system (SNS) activity due to cold stress.

Keywords: ^{18}F-Fluorodeoxyglucose – Positron emission tomography – X-Ray computed tomography – Image co-registration – Fatty tissue

Eur J Nucl Med (2002) 29:1393–1398
DOI 10.1007/s00259-002-0902-6

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Introduction

Fluorine-18 fluorodeoxyglucose positron emission tomography (FDG PET) has been introduced into clinical routine mainly for oncological imaging. Physiological FDG activity is present in the brain, the kidney and the urinary collecting system [1]. FDG uptake has been described in various malignancies, mainly carcinomas, lymphomas and melanomas. However, FDG uptake is not tumour specific, and a variety of artefactual and physiological sources of FDG accumulation have been identified. Inflammatory cells and statically or dynamically exercised muscle are among the most frequent sites of uptake in addition to tumour tissue [2]. Several authors have described specific patterns of physiological and non-specific FDG uptake [1, 3]. Barrington et al. in particular reported a distinctive pattern of symmetrical

uptake in the neck and paravertebral region of the thoracic spine [1, 3]. This uptake was regarded as muscular uptake since it disappeared after the application of muscle relaxants in repeated scanning.

In PET imaging, missing landmarks impede exact localisation. The introduction of co-registered imaging now permits exact localisation of FDG uptake. The purpose of this study was to re-evaluate by means of PET/CT images the aforementioned distinct FDG uptake pattern, which has hitherto been thought to be of muscular origin in most patients. We describe our findings in 17 patients with symmetrical neck, shoulder and thoracic spine uptake in a series of 638 patient studies performed with PET/CT and discuss the possible pathophysiological causes.

Materials and methods

Between April and November 2001, 638 consecutive patients referred for PET/CT were imaged on an in-line PET/CT system. All PET examinations were evaluated retrospectively for increased, symmetrical FDG uptake within the neck, thorax and shoulder regions by two board-certified nuclear physicians (E.G. and G.v.S.) and the exact location of the FDG uptake was determined in co-registered PET/CT images.

Data acquisition. All imaging and data acquisition was performed on a combined PET-CT system (Discovery LS, GE Medical Systems, Waukesha, Wis., USA), able to acquire CT images and PET data of the same patient in one session. A GE Advance NXi PET scanner and a multidetector-row helical CT (LightSpeed plus) were integrated in this dedicated system. The table excursion permitted scanning of six contiguous PET sections covering 867 mm. This gave adequate coverage from the head to the pelvic floor in all patients examined. The axes of both systems were mechanically aligned to coincide. The offset between the CT and PET scanner sensitive field of views along the table axis was 60 cm. The PET and CT data sets were acquired on two independent computer consoles, which were connected by an interface to transfer CT data to the PET scanner. For viewing of the images, which came off the system in a co-registered manner, the PET and CT data sets were transferred to an independent, PC-based computer workstation by DICOM transfer. While PET images were acquired during free breathing and each image was acquired over multiple respiratory cycles, CT scans were acquired during shallow breathing.

Prior to the examination, patients were fasted for at least 4 h before the intravenous administration of 10 mCi (370 MBq) of FDG. Forty-five minutes after the injection, the combined examination was commenced. CT data were acquired first. The patient was positioned on the table in a head-first, supine position. Start and end locations were chosen carefully to ensure coverage of the entire body region of interest, from the level of the cerebellum to the pelvic floor. The arms of the patients were placed in an elevated position above the abdomen to reduce beam-hardening artefacts at the level of the liver. However, in patients unable to obtain this position, arms were positioned in front of the abdomen. For the CT data acquisition, the following parameters were used: tube rotation time 0.5 s/evolution, 140 kV, 80 mA, 22.5 mm/rotation, slice pitch 6 (high speed mode), reconstructed slice thickness 5 mm, scan length 867 mm, acquisition time 22.5 s per CT scan.

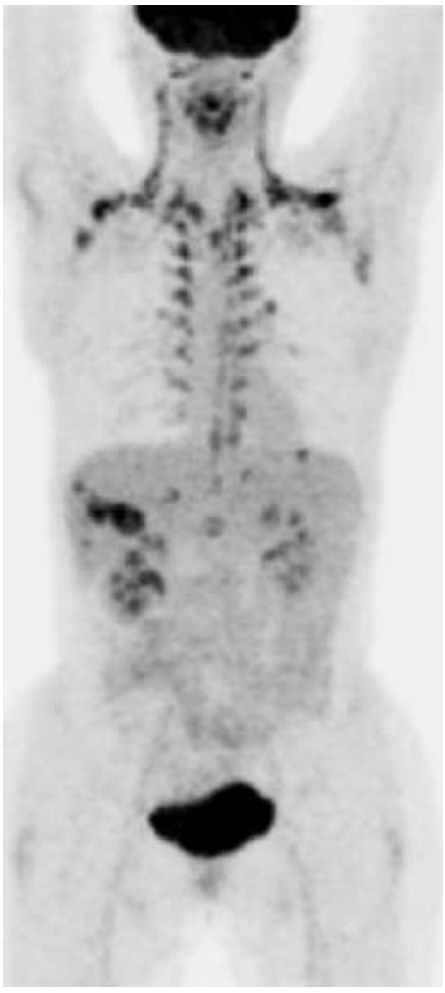

Fig. 1. Maximum intensity projection (MIP) PET image in a 42-year-old female patient with known liver and pulmonary metastases of a breast cancer shows typical symmetrical enhancement in the neck, shoulder and thoracic spine region

After the CT data acquisition had been completed, the table top with the patient was automatically advanced into the PET gantry and acquisition of PET emission data was started at the level of the pelvic floor. Six incremental table positions, each 146 mm wide, were acquired with minimal overlap, thereby covering 867 mm of table travel. For each position, 35 2D non-attenuation-corrected scans were obtained simultaneously over a 5-min period. No transmission scans were obtained since CT data were used for attenuation correction. The technique for using CT data for attenuation correction has been described in detail elsewhere [4]. Transaxial, attenuation-corrected slices were reconstructed using iterative reconstruction. The image reconstruction matrix was 128×128, with a transaxial field of view of 49.7×49.7 cm.

Image analysis. All viewing of co-registered images was performed with dedicated software (eNTEGRA, ELGEMS, Haifa, Israel). No post-processing such as re-alignment of PET and CT data was necessary since both systems are mechanically aligned. Co-registered images of the patients with symmetrical uptake in the neck-shoulder-upper thoracic spine region on PET maximum intensity projection images were re-evaluated and exact localisation

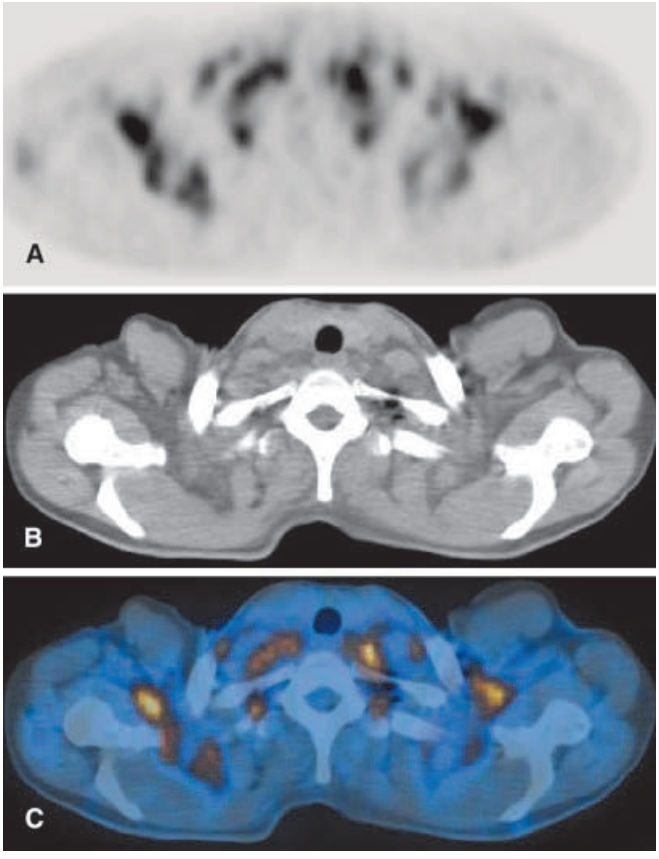

Fig. 2. Axial PET (**A**), CT (**B**) and co-registered PET/CT images in the same patient as in Fig. 1. The symmetrical FDG uptake is located within the fatty tissue, not the muscles (**C**)

of FDG uptake was determined (muscle, bone, fatty tissue or articulation). Uptake on transmission-corrected images was subjectively determined on a four-point scale: 1, general soft tissues including inactivated muscle; 2, liver; 3, more than liver but less than brain; 4, brain.

Patient data analysis. The selected patients were analysed with regard to the following criteria: age, gender, diagnosis, time since end of therapy, body mass index, medication and body posture during scanning.

Results

In 17 of the 638 patients (2.5%), increased, symmetrical FDG uptake was found in the shoulder region that was not related to muscular structures on CT.

Two patterns could be distinguished. One pattern showed FDG uptake in the lower part of the cervical spine, the shoulder region and the upper thoracic spine in the costovertebral region at levels equalling brain uptake (average 3.4). The other pattern showed only intermediate uptake of FDG limited to the shoulder region (average 2.8). In all patients, the soft tissue uptake was clearly

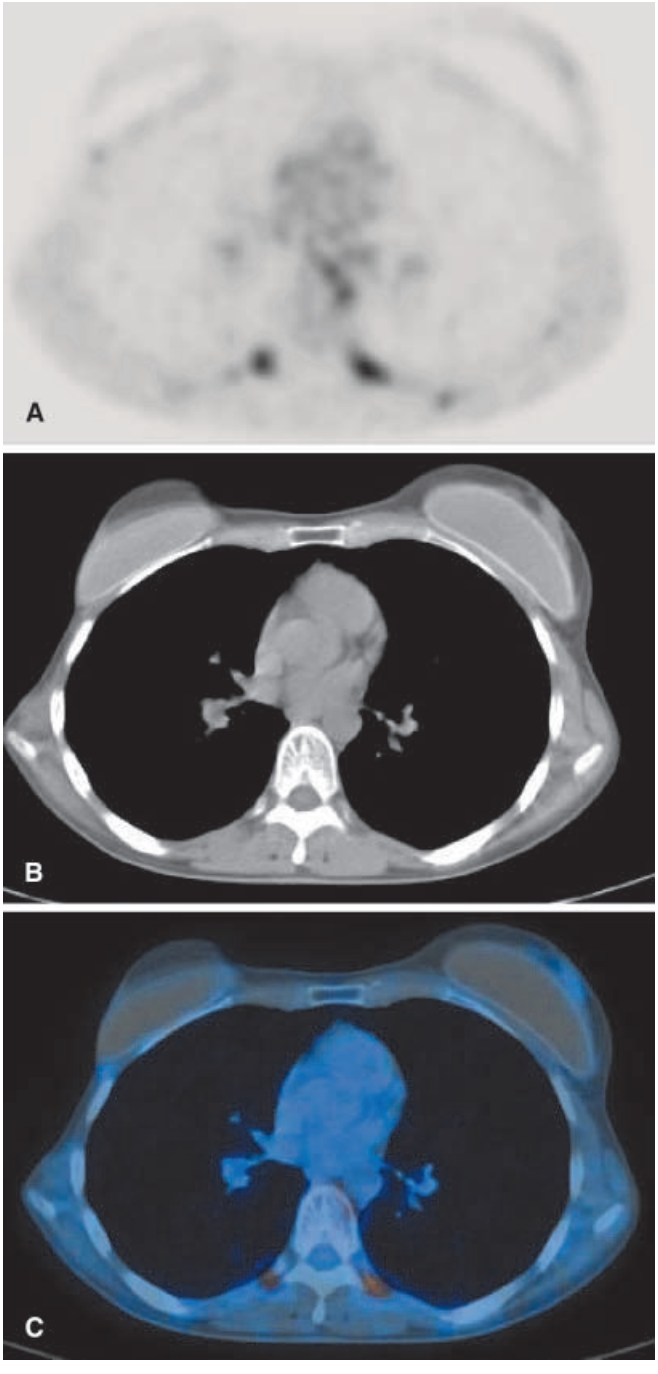

Fig. 3. Axial PET (**A**), CT (**B**) and co-registered PET/CT images in the same patient as in Fig. 1. FDG is located in the soft tissue in the region of the costovertebral joints (**C**)

localised within the non-muscular soft tissue of the neck and shoulders (Figs. 1, 2). The uptake in the region of the thoracic spine was localised in the area of the costovertebral joints (Figs. 3, 4), where muscular, fatty, bone and joint structures are closely associated, precluding clear assignment of the FDG activity to one of these tissues.

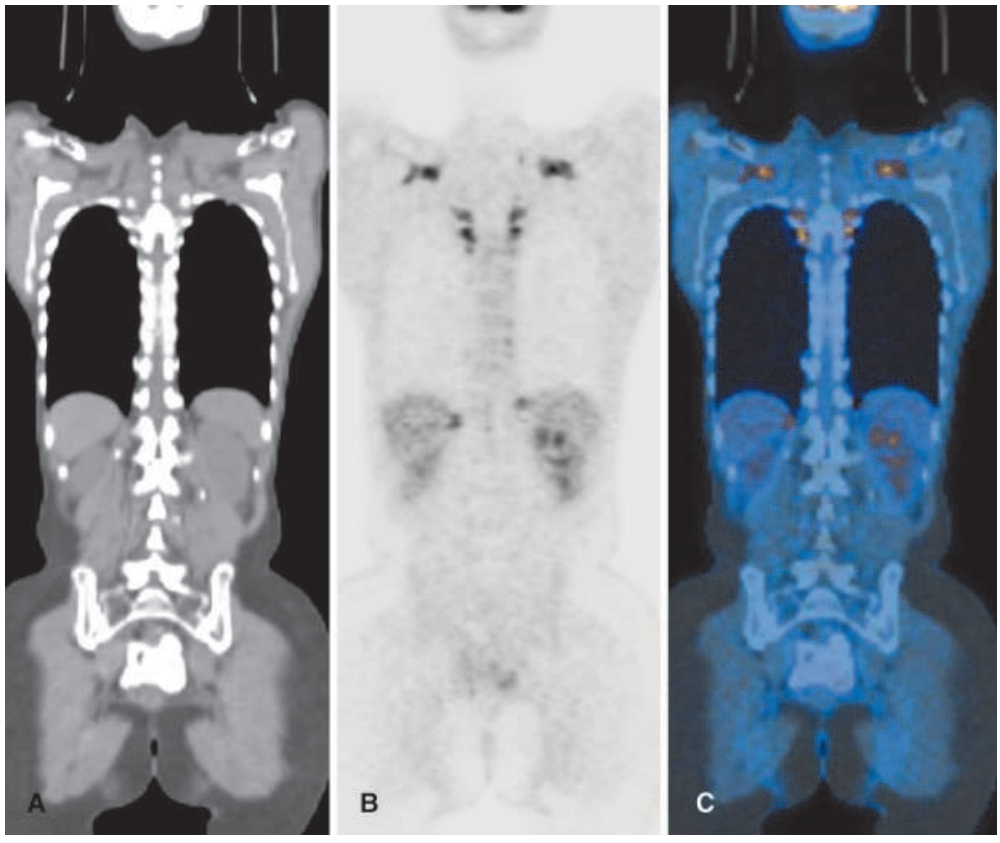

Fig. 4. Coronal CT (**A**), PET (**B**) and co-registered PET/CT (**C**) images in the same patient as in Fig. 1 again show clear localisation of bilateral FDG uptake in the fatty tissue of the shoulders and intercostal region

The pattern of high uptake in the neck, shoulder and spine was seen in seven female patients (32.3 years). The average body mass index (BMI) was 19.0 (range 16.8–23.4) (below 18.5= underweight; 18.5–24.9= normal; 25.0–29.9= overweight, above 30= obesity) [5]. In four of these seven patients, the BMI was below 18.5. In the other ten patients (two male, eight female, average age 37.1 years), the average BMI was 22.7 (18.7–27.7).

The underlying diagnoses in the 17 patients were: breast cancer (*n*=4), Hodgkin's lymphoma (*n*=4), non-Hodgkin's lymphoma (*n*=2), lung cancer (*n*=1), gastrointestinal stromal tumour (*n*=1), infectious disease (*n*=1), neuroendocrine tumour (*n*=1), vulvar carcinoma (*n*=1), hypopharyngeal carcinoma (*n*=1), uterine carcinoma (*n*=1).

Discussion

The results of this study indicate that symmetrically increased FDG uptake in the neck, shoulder region and thoracic spine may also be localised within the non-muscular soft tissue as well as in musculature. Co-registered PET/CT imaging allows for the exact localisation of pathological FDG uptake. In cases of symmetrically increased FDG uptake – starting in the neck, proceeding vertically downwards, and extending from the lower neck first laterally and then caudally in the mid-axillary line – the uptake could unambiguously be localised in non-muscular soft tissue rather than muscle tissue. In a little over half of the patients the extent of fatty uptake was limited to the lower neck and shoulder region.

In a previous study it was claimed that the observed uptake pattern was attributable to muscle since administration of diazepam, a muscle relaxant, led to reduction or disappearance of FDG uptake on a second scan performed 8 days to 6 weeks after the initial baseline study [3].

In our PET/CT study, the described pattern of increased FDG uptake was found not to be related only to muscular FDG uptake. Analysis of our results revealed two different patterns of uptake, which were also noted in the previous study. One patient group with FDG uptake in the neck, shoulder and thoracic spine region had a clearly decreased average BMI. In four of these seven patients the BMI was lower than 18.5. In the other group with only intermediate uptake in the shoulder region, BMI was in the normal range. In one patient, PET imaging was performed 2 years before the introduction of PET/CT, and showed the typical symmetrical FDG uptake. The identical pattern was demonstrated by PET/CT imaging twice at an interval of 6 months.

From a technical point of view, a theoretical misalignment in co-registration can be postulated. However, the shoulders as well as the thoracic spine are rather stable anatomical structures without extensive motion during

breathing. Arm movement during CT and PET acquisition can be recognised. Mechanical misalignment related to mechanical parts of the PET and CT scanners might also be postulated. However, weekly quality controls with an alignment phantom under weight bearing has not revealed any major misalignments to date, and a systematic mistake in one spatial direction could not be detected in any of the 17 studies.

Several possible reasons can be proposed for the finding that the FDG uptake noted was related not to muscular activity but rather to FDG accumulation in non-muscular soft tissue. This soft tissue contains vessels, adipose tissue and peripheral nerves. The adipose tissue contains white (WAT) and brown adipose tissue (BAT) [6]. The presence of brown adipose tissue in the human has been described in infants as well as adults. Its extension seems to vary widely but corresponds to the locations seen in our patients [7]. BAT necrosis has been described in infants with congenital heart disease [8]. Interestingly, patterns in such cases are identical to those seen in our patient population [8]. It is also to be noted that BAT accumulation is increased in underweight patients [9].

It is well known that temperature control in rodents as well as in infants in the fasting state is regulated via BAT [6, 10, 11, 12]. Glucose turnover in correspondence with the energy balance reveals that in BAT lipids are the primary source of energy, which are directly translated into heat. The BAT mitochondria operate in an uncoupled mode, that is, they reduce markedly their production of adenosine triphosphate (ATP) and increase their oxidation of fatty acids, thus increasing heat production. To compensate for the uncoupling, and to prevent the BAT becoming ATP deficient, metabolism of glucose via anaerobic glycolysis is increased. This results in regeneration of ATP from adenosine diphosphate (ADP) and in the production of lactate, which is exported to the liver for re-conversion to glucose. BAT generates 2-ATP for vital cytosolic processes which would otherwise stop (e.g. fatty acid activation, which must occur for fatty acid oxidation to proceed), whereas liver uses 6-ATP to regenerate the glucose. Glucose is not a major fuel for thermogenesis in BAT, since it is not itself oxidised but is transformed to lactate and exported. Therefore glucose is essential for continued thermogenesis that uses fatty acids as fuel because it allows the generation of ATP needed for activation of these fatty acids [13]. Even though the room temperature in the uptake and scanner room is around 22.5ºC, people with a low BMI are more prone to feel cold, leading to non-shivering thermoregulation by stimulation of the sympathetic nerve system (SNS) [14]. SNS activity significantly increases glucose uptake by BAT itself [15, 16, 17]. Therefore, symmetrical FDG uptake could be interpreted as due to non-shivering thermoregulation that involves a direct increase in glucose uptake by BAT caused by SNS activity and the need for glucose to maintain the process of lipolysis, as described above.

Paravertebral FDG uptake has been visualised mostly in patients with a lower-than-normal BMI index. The cold stress in this patient population is more prominent, and recruitment of further BAT deposits along the thoracic spine could be postulated. On the other hand, especially in the thoracic spine region, shivering due to fasciculation of muscular structures could be postulated and the paraspinal uptake could represent muscular uptake.

For ethical reasons, tissue confirmation by biopsy was not possible. Gender also seems to be correlated with the incidence of the described uptake pattern, which is especially frequent in women with a low BMI.

The symmetrical FDG uptake can potentially mimic pathological uptake due to malignancy. As postulated in the study by Barrington and Maisey [3], administration of diazepam can reduce the observed uptake pattern. Diazepam has some dampening influence on the SNS, which could explain the resulting reduction in uptake. Since diazepam does not specifically block the SNS, the administration of agents that do specifically block the SNS, such as beta-blockers, may be useful in further studies to evaluate this symmetrical FDG uptake. Another approach could be a cold challenge in a controlled study to reproduce the uptake pattern.

In conclusion, symmetrical FDG uptake in the shoulder, neck and thoracic spine region is probably not related solely to muscular uptake but also to uptake by fatty tissue.

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