Concise report

Positron emission tomography/computed tomography: a clinical tool for evaluation of enthesitis in patients with spondyloarthritides

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Abstract

Objective. To evaluate the accuracy of PET/CT using [¹⁸F]fluorodeoxyglucose (FDG) in determining the presence of enthesitis in patients with SpAs.

Methods. Results of PET/CT scans of eight patients with SpA and seven patients with RA were retrospectively examined, with specific focus on five joints and three entheses. Volume fixation values are expressed as standardized uptake values (SUVs). Data from 20 patients with non-rheumatic (NR) diseases and 20 healthy subjects were also examined if non-specific, false positive findings were possible. We evaluated the clinical utility of PET/CT examinations in SpA, compared with MRI and Ga scintigraphy.

Results. Images of PET/CT scans of the shoulder, hip and knee joints revealed that FDG accumulated at the entheses in SpA and in the synovium in RA patients. The maximum SUVs [mean (s.d.)] were statistically higher in SpA patients compared with RA patients at the entheses of lumbar spinous process [4.83 (1.15) vs. 1.42 (0.34); \( P < 0.05 \), respectively], public symphysis [3.93 (0.87) vs. 1.35 (0.31); \( P < 0.05 \), respectively] and ischial tuberosity [4.76 (1.5) vs. 1.35 (0.42); \( P < 0.05 \), respectively]. The positive frequencies of lumbar spinous processes and ischial tuberosity evaluated by PET/CT scan in the SpA group were significantly higher than that evaluated by MRI.

Conclusion. MRI is now widely used to detect bone marrow oedema and enthesitis in patients with SpA. PET/CT scans offer an alternative method to identify enthesitis, and will likely contribute to the early diagnosis of SpA.

Key words: [¹⁸F]fluorodeoxyglucose PET/CT, Enthesitis, Spondyloarthritides, Rheumatoid arthritis.

Introduction

SpAs include AS, PsA, ReA, enteropathic arthritis and uSpA [1]. SAPHO syndrome was recently recognized as a subtype of SpA [2]. SpAs often involve the entheses [3] and are often associated with the presence of HLA-B27 [4]. SpAs occur mainly in young patients, but later onset of SpA can also occur [5].

Entheses are sites where tendons, ligaments or joint capsules attach to bone, and enthesitis is another characteristic feature of SpA. Enthesitis results in new bone proliferation, providing the basis for eventual bony ankylosis [6]. The diagnosis of SpA is mainly based on the history, physical examination and plain X-ray or MRI examination. The diagnosis of early-stage SpA is important with regard to treatment, prognosis and evaluation of disability in these patients.

PET/CT with [¹⁸F]fluorodeoxyglucose (FDG) is mainly used in diagnosing malignancy, staging and monitoring changes in response to treatment [7]. PET/CT images offer metabolic images at a precise FDG-uptake point.
based on high-quality CT images. Up to 29% of the total amount of FDG injected is not taken up by tumour cells, but by macrophages and surrounding granulation tissue [8]. These findings, and the fact that TNF-α enhances glucose entry and transport into macrophages [9], are arguments for the use of FDG-PET to detect and monitor the disease activities. In fact, it was recently reported that PET/CT can be used to assess sarcoidosis [10], RA [11] and GCA [12], in addition to investigating patients with fever of unknown origin [13].

Only two case reports have shown that PET/CT is beneficial for the diagnosis of PsA [14] and AS [15]. In the present study, we retrospectively evaluated the clinical utility of PET/CT for the diagnosis of enthesitis and/or arthritis in patients with SpA or RA.

Patients and methods

Patients and enrolled healthy subjects

All of the patients were referred between January 2006 and September 2008 to our clinic for further examination of polyarthralgia, fever of unknown origin and/or tumour. These 35 patients had SpA, untreated RA or non-rheumatic (NR) diseases, and all patients received PET/CT examination to exclude malignancy. A further 20 healthy subjects who underwent PET/CT examination had personally requested health checks for excluding malignancy. The present study is a retrospective one. Prior to the PET/CT examinations, written informed consent approved by Kochi Medical School Hospital was obtained from all of the patients and healthy subjects. The present study was conducted in accordance with the Declaration of Helsinki. We used the Amor criteria for the diagnosis and classification of SpA [16]. Eight patients were diagnosed with SpA.

Characteristics of the enrolled subjects

The ages [mean (s.d.)] of patients with SpA, RA, NR and healthy subjects were 65 (11), 63 (10), 60 (13) and 64 (4) years, respectively. Numbers of males/females were 5/3, 2/5, 5/15 and 12/8, respectively. Laboratory data (excluding healthy subjects) of serum CRP were 8.2 (4.9), 4.5 (2.1) and 1.3 (2.4) mg/dl and ESR were 115 (46), 89 (30) and 48 (35) mm/h, respectively. The eight SpA patients with arthralgia, back pain and buttock pain lasting for 1–8 months, included one with SAPHO syndrome (69 years old), one with PsA (72 years old), two with AS (48 and 50 years old), three with uSpA (73, 73 and 76 years old) and one with ReA (63 years old). HLA-B27 was demonstrated in two (25%) of the eight patients with SpA. Seven patients with RA were presented as cases 9–15. Twenty patients, defined as the NR group, presented with the following diseases: acromegaly, viral infection, thyroid cancer, autoimmune hepatitis, malignant lymphoma, colon cancer, pancreatic cancer, multiple myeloma, adrenal tumour, uterus cancer, parotid gland tumour and chronic GN.

Study design

In the present study, we retrospectively investigated the clinical implications of PET/CT scans. The data of PET/CT in the Department of Radiology, Kochi Medical School Hospital, obtained between January 2006 and October 2008 were consecutively collected, and the data of patients with eight SpA, seven RA, 20 NR and 20 healthy controls were consecutively analysed. As mentioned, subjects who had diabetes mellitus according to the American Diabetes Association criteria [17] were excluded. We evaluated the intensity of FDG accumulation in the spots in the PET/CT scans [volume fixation values were expressed as standardized uptake values (SUVs)] in patients with SpA, RA or NR and in healthy subjects. The SUV is defined as the tissue concentration divided by the activity injected per body weight. The reliability of PET/CT for the identification of enthesitis and for calculation of SUV was determined. Our co-authors, two nuclear medicine specialists (M.F. and T.O.), measured the maximum SUV in each of the entheses. We compared the values among the groups. In the SpA group, the sensitivities (positive frequencies) were also compared among the PET/CT, MRI and Ga scintigraphy scans.

PET/CT examination

Whole-body PET/CT examination was performed with a combined PET/CT scanner (Discovery STE; GE Healthcare, Milwaukee, WI, USA). The PET/CT technique in the present study has been previously described [18]. The technical parameters used for the CT portion of PET/CT were as follows: a detector row configuration of 14 x 1.25 mm, pitch 1.75: 1 (middle-speed mode). A whole-body emission PET scan was performed for the same axial coverage as was performed with a 2–3-min acquisition period for each bed position. In our clinic, the average irradiation dose of FDG-PET/CT is <10 mSv (the irradiation doses of FDG-PET or combined CT are 3–5 and 5 mSv, respectively), whereas irradiation dose of usual CT is 15 mSv.

All patients fasted for at least 6 h before the PET/CT scan. One hour before imaging, a weight-adjusted dose of FDG was injected intravenously [dose (MBq) = weight (kg) x 3.5]. All images from PET/CT scans were reviewed by two nuclear medicine specialists, who were blinded to the patients’ details and clinical characteristics.

MRI and Ga scintigraphy examinations

Six patients had MRI and three had Ga scintigraphy examinations. All of the MRI and Ga scintigraphy images were also reviewed by two nuclear medicine specialists who were blinded for the PET/CT data.

Statistical analysis

All values are presented as mean (s.d.). A comparison of variables between two groups or among more than three groups was performed using a Mann–Whitney U-test or one-way analysis of variance. The sensitivities (positive frequencies) of the examinations were estimated using chi-square tests. Statistical analysis was performed...
using a software program (JMP, version 7; SAS Institute Inc., Cary, NC, USA). Results were considered significant for \( P < 0.05 \).

**Results**

**PET/CT images of SpA**

In patients with NR and in healthy subjects, there was no significant uptake of FDG in the joint regions. Therefore, we confirmed no pseudo-positive findings in the joint and enthesis regions. The typical horizontal and frontal slices showed significantly high FDG uptake in the sternoclavicular joints (Fig. 1B), lumbar spinous processes (Fig. 1C), SI joints (Fig. 1D), pubic symphysis (Fig. 1F) and the ischial tuberosity (Fig. 1G) in patients with SpA. However, there was no uptake in similar regions in the RA group. Moreover, highly positive FDG uptake in the shoulder (Fig. 1A), hip (Fig. 1E) and knee joints (Fig. 1H) were observed in both the RA and SpA groups. However, differences in the distribution of FDG accumulation between RA and SpA groups were observed, notably in the IA synovial area in the RA group. In contrast, in the

**Fig. 1** Comparison of PET/CT findings between the RA and SpA groups. Enthesitis can be seen in the SpA group in the shoulder joints (A), sternoclavicular joints (B), lumbar spinous processes (C), SI joints (D), hip joints (E), pubic symphysis (F), ischial tuberosity (G) and knee joints (H). Enthesitis is not seen in the RA group.
SpA group, accumulation mainly occurred on the enthesis portion of the ligaments, articular capsules of the femur, coxal and humerus bones, and the shoulder blade. Considering the location of the entheses in the articular joints, it was apparent that FDG accumulation was consistent with entheses in SpA, but with the synovium in RA.

Measurement of SUV in PET/CT scans

In the healthy subjects and in the NR and RA groups, statistical significance of the maximum SUV for the evaluated areas was found in the shoulder and hip joints. The maximum SUV for the sternoclavicular joints, lumbar spinous processes, SI joints, pubic symphysis and ischial tuberosity were significantly higher in the SpA group compared with the RA group (Fig. 2).

Sensitivity of positive detection using PET/CT examination in SpA

The sensitivities to detect enthesitis using PET/CT examination were significantly high in the SpA group (Table 1). The positive frequencies of FDG accumulation in the shoulder, hip and knee joints using PET/CT scan were
high in both the RA and SpA groups. However, we could clearly differentiate the RA group from the SpA group by evaluating the positive frequencies for the sternoclavicular joints, lumbar spinous processes, SI joints, pubic symphysis and the ischial tuberosity obtained using PET/CT scans.

Interestingly, the sensitivity of PET/CT was significantly higher than for MRI in the lumbar spinal processes and the ischial tuberosity (Table 1). Ga scintigraphy also showed lower sensitivity than PET/CT (Table 1).

Clinical course of SpA evaluated by PET/CT scan
We confirmed the clinical utility of PET/CT scan before and after treatments. In an SpA case, the strong FDG accumulation in entheses was significantly reduced by the evaluation of both image and SUV analysis 3 months after the treatment of celecoxib 400 mg daily, MTX 6 mg weekly, prednisolone 10 mg daily and salazosulfapyridine 1000 mg daily (data not shown).

Discussion
The rate of HLA-B27 was 25% in the present study. The small proportion of patients with HLA-B27 in the SpA group might be due to racial differences; 7–14% of Caucasians and >1% of the Japanese population are positive for HLA-B27 [19]. It has been reported that the majority of HLA-B27-negative Japanese patients with AS have HLA-B39 (3/8 positive in the present study), which is molecularly homologous to HLA-B27 [19]. Therefore, AS is a rare disease in Japan, and only two AS patients were part of our study. The average age of our SpA patients was high; this was attributed to the patients with SAPHO syndrome, PsA, uSpA and ReA in the SpA group.

The findings reported in SpA by MRI indicate that the earliest inflammatory changes are best observed with MRI and include the inflammatory appearance of the ligaments and their insertions [20]. In addition, MRI has been extensively used to evaluate the spine in patients with AS,
before and after successful therapy with infliximab [21] or etanercept [22]. Whole-body MRI has recently been used as a screening tool to detect axial and peripheral manifestations of SpA [23]. However, we could not determine whether MRI was sensitive in the present study.

While radiographs of SpA are often normal when the symptoms first develop, there is often an unacceptable delay between the onset of symptoms and the time of diagnosis for SpA. As a result, the treatment is often inadequate or ineffective [24]. Some recent reports have shown that TNF blockers did not prevent new bone formation, although inflammation was effectively suppressed [25]. It was indicated that new bone formation could be prevented if TNF blocker treatment is started early enough, and before the onset of erosive structural damage [26].

On examining the PET/CT findings of the present study, the regions with high FDG accumulation in SpA corresponded to the following entheses: (i) the coracohumeral and coracoclavicular ligaments and the joint capsule in the shoulder; (ii) the anterior sternoclavicular and interclavicular ligaments in the sternoclavicular joints; (iii) the interspinous, supraspinous and lateral costotransverse ligaments in the lumbar spinous processes; (iv) the iliofemoral, ischiofemoral and pubofemoral ligaments, the piriform and gluteus minimus muscles and the joint capsule in the hip; (v) the superior pubic and arcuate pubic ligaments in the pubic symphysis; (vi) the sacrotuberous and sacrospinous ligaments in the ischial tuberosity; and (vii) the hamstring muscles and joint capsule in the knee. The regions of FDG accumulation in SpA were different from RA and these findings are of great interest for evaluating the performance of PET/CT.

Moreover, our results indicate that PET/CT had higher sensitivity for evaluating enthesitis than MRI or Ga scintigraphy. In patients with SpA, the frequency of negative MRI and positive PET/CT findings for the lumbar spinous process enthesis and the ischial tuberosity enthesis was 2/3 cases (66.6%) and 3/5 cases (60%), respectively. In contrast, the frequency of negative Ga scintigraphy and positive PET/CT for the lumbar spinous process, ischial tuberosity and sternoclavicular joint enthesis was 3/3 cases (100%), 3/3 cases (100%) and 2/3 cases (100%), respectively (Table 1). Importantly, the frequency of negative PET/CT and positive MRI or Ga scintigraphy in SpA was 0% for each enthesis. The results mean that PET/CT scanning might at least have sensitivity and specificity that are equivalent or superior to MRI in the SpA group. Furthermore, the ability to perform PET/CT for the whole body in one scan offers a considerable clinical advantage for extensive assessment of enthesitis.

A limitation of the present study is its retrospective design. The lack of mechanical control group, such as sportive patients with traumatic pain of tendon insertion would be a great argument for supporting the enthesitis accumulation as a landmark of inflammatory process and for suggesting the use PET/CT for diagnostic purpose. A cross-sectional study could be needed. The evaluation of scans before and after treatment in SpA could have also been conducted prospectively in a larger number of patients.

In conclusion, the present study confirms that PET/CT scanning offers an alternative method to the currently used techniques to identify enthesitis, and will contribute to the early diagnosis of SpA patients, although MRI is now widely used to detect bone marrow oedema and enthesitis in SpA patients. The use of PET/CT is particularly advantageous for the diagnostic investigation of atypical SpA, and differentiation of SpA from RA. Moreover, PET scanning could also be used to investigate the whole-body inflammation in a single session. We suggest that popularization of PET/CT might contribute to the diagnosis of SpA and evaluation of disease activity after treatment. Therefore, there is a need to conduct a large-scale prospective study of PET/CT for SpA.

### Table 1: Sensitivity of detecting enthesitis using PET/CT, MRI and Ga scintigraphy

<table>
<thead>
<tr>
<th>Enthesis</th>
<th>Healthy subjects, n/N (%)</th>
<th>NR, n/N (%)</th>
<th>RA, n/N (%)</th>
<th>SpA, n/N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shoulder</td>
<td>0/20 (0)</td>
<td>0/20 (0)</td>
<td>7/7 (100)</td>
<td>7/8 (87.5)</td>
</tr>
<tr>
<td>Sternoclavicular joints</td>
<td>0/20 (0)</td>
<td>0/20 (0)</td>
<td>1/7 (14.2)</td>
<td>6/8 (75)*</td>
</tr>
<tr>
<td>Lumbar spinous process</td>
<td>0/20 (0)</td>
<td>0/20 (0)</td>
<td>0/7 (0)</td>
<td>7/8 (87.5)*</td>
</tr>
<tr>
<td>SI joints</td>
<td>0/20 (0)</td>
<td>0/20 (0)</td>
<td>0/7 (0)</td>
<td>6/8 (75)*</td>
</tr>
<tr>
<td>Hip</td>
<td>0/20 (0)</td>
<td>0/20 (0)</td>
<td>6/7 (85.7)</td>
<td>7/8 (87.5)</td>
</tr>
<tr>
<td>Pubic symphysis</td>
<td>0/20 (0)</td>
<td>0/20 (0)</td>
<td>0/7 (0)</td>
<td>5/8 (62.5)*</td>
</tr>
<tr>
<td>Ischial tuberosity</td>
<td>0/20 (0)</td>
<td>0/20 (0)</td>
<td>0/7 (0)</td>
<td>6/8 (75)*</td>
</tr>
<tr>
<td>Knee</td>
<td>(–)</td>
<td>(–)</td>
<td>2/2 (100)</td>
<td>2/2 (100)</td>
</tr>
</tbody>
</table>

Frequencies of FDG accumulation in healthy subjects and non-arthritis showed 0% in all regions. *P < 0.05 compared with positive frequencies of PET/CT in RA group (chi-square test). **P < 0.05 compared with positive frequencies of MRI in SpA group (chi-square test). In knee joints, cohorts were too small to allow valid statistical analysis. (–); positive frequencies of the knee in healthy subjects and non-arthritis could not be evaluated as the knee is not evaluated routinely in PET/CT. ND: not done. NA: not available.
References


