Does antibiotic treatment affect the diagnostic accuracy of FDG PET/CT studies in patients with suspected infectious processes?

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ABSTRACT

Fluoro-deoxyglucose positron emmission tomography combined with computed tomography (FDG PET/CT) plays a significant role in the assessment of various infectious processes. Patients with suspected or known sites of infection are often referred for FDG imaging while already receiving antibiotic treatment. Current study assesses whether antibiotic therapy affects the detectability rate of infectious processes by FDG PET/CT.

Methods: A 5-year retrospective study of all adult patients who underwent FDG PET/CT in search of a focal source of infection was performed. The presence, duration and appropriateness of antibiotic treatment prior to FDG imaging were recorded. Diagnosis of an infectious process was based on microbiological and/or pathological data as well as on clinical and radiological follow-up.

Results: Two hundred seventeen patients underwent 243 PET/CT studies in search of a focal source of infection and were included in the study. Sixty seven studies were excluded from further analysis because of a final non-infectious etiology or lack of further follow up or details regarding the antibiotic treatment. The final study population included 176 FDG PET/CT studies in 153 patients (M 107, age 18-86 years). One hundred nineteen studies (68%) were performed in patients receiving antibiotic therapy for a range of 1 to 73 days. Diagnosis of infection was made in 107 true positive cases (61%) including 63 studies (59%) in patients receiving appropriate antibiotic therapy started before the performance of the FDG PET/CT study. There were 52 true negative
(29%) and 17 false positive (10%) FDG PET/CT studies. No false negative results were found.

**Conclusion:** FDG PET/CT correctly identified foci of increased uptake compatible with infection in the majority of patients including all patients receiving appropriate antimicrobial therapy, with no false negative cases. Based on current study results administration of antibiotics appears to have no clinically significant impact on the diagnostic accuracy of FDG PET/CT performed for evaluation of known or suspected infectious processes.

Key words: FDG PET/CT, antibiotic therapy, infectious process
INTRODUCTION

In recent years there is increasing literature evidence regarding the role of FDG PET/CT in the evaluation of various infectious and aseptic inflammatory disorders (1). Accumulation of F18 FDG in infectious processes is due to the fact that activated leukocytes exhibit high amounts of glucose transporter proteins on the cell membrane (2,3). Patients with suspected bacterial infections are often started on antibiotic treatment before a definite focus of infection has been identified. Thus, the clinical setting when patients with suspected infections undergo FDG PET/CT study while already receiving antibiotic therapy is not rare.

White blood cells labeled with Tc99m-HMPAO or In11-oxine has been the gold standard nuclear medicine procedure for diagnosis of various infectious processes in the era prior to FDG PET/CT. Some publications have addressed the issue of a potential effect of antibiotic therapy on leukocyte chemotaxis in vitro and on the sensitivity of labeled white blood cells scans with conflicting results (4,5).

To the best of our knowledge the potential effect of antibiotic treatment on the uptake of FDG is not well established. Current study aims at assessing whether antibiotic therapy affects the detectability rate of infectious processes by FDG PET/CT.
MATERIALS AND METHODS

Patient Population

The study population included all adult patients investigated for suspected infectious process and assessed by FDG PET/CT over the years 2010-2015. The indications for referral included suspected musculo-skeletal, vascular graft and polycystic kidney infection, as well as patients with fever of unknown origin and bacteremia evaluated in search of a focal source of infection. Patients were identified by reviewing FDG PET/CT referrals over this period. The Institutional Review Board approved this retrospective study and the requirement to obtain informed consent was waived. Patient files were reviewed for clinical data at the time of imaging. Administration of antibiotic treatment prior to performing the FDG PET/CT study was recorded. In patients receiving antibiotic treatment, the duration prior to the PET/CT study and route (intravenous or oral) of administration were recorded. Antimicrobial therapy was considered to be appropriate if administered according to the susceptibility of the specific type of pathogen diagnosed by microbiologic tests or if it led to clinical improvement in cases with no microbiologically documented infection. When these criteria were not met antibiotic treatment was defined as inappropriate and patients in this subgroup were considered as not treated in further analysis. The final diagnosis of an infectious process was based on microbiological and pathological data as well as on clinical and imaging follow-up.

PET/CT Acquisition
Patients were instructed to fast, except for glucose-free oral hydration, for at least 4 hours before the injection of 185-592 MBq (5-16 mCi) of FDG. The patients kept their regular drug schedule. Oral contrast was administered selectively. Patients evaluated for fever of unknown origin, bacteremia and suspected polycystic kidney infection underwent eye-to-mid-thigh PET/CT acquisition with lower limb scanning added when clinically indicated. Patients investigated for suspected musculo-skeletal and vascular graft infection were scanned according to the clinical area of interest. PET/CT (Discovery 690; GE Healthcare) images were acquired 60 minutes after the injection of the radiopharmaceutical and reviewed in axial, coronal, and sagittal planes on a dedicated workstation (Xeleris, GE Healthcare).

**Interpretation and Analysis of PET/CT Images**

All studies were reviewed by two nuclear medicine physicians with knowledge of the clinical history and of results of previous imaging studies but unaware whether antibiotic treatment had been administered. Studies showing at least one site of FDG uptake with intensity higher than that of surrounding tissues, localized to an area that did not correspond to the physiologic biodistribution of the tracer, were defined as positive. Studies showing FDG activity only in areas of physiologic tracer distribution were defined as negative. A positive FDG PET/CT study in a patient further confirmed as having a focal active infectious process was defined as true-positive (TP). A positive FDG study in patients with no final diagnosis of focal infection or with pathology identified in a location different from the site demonstrated on PET/CT was defined as false positive (FP). A negative PET/CT study was true-negative if no localized infectious
process was further diagnosed while in patients with further evidence of an active infection it was defined as false-negative (FN).

Maximum standardized uptake values (SUVmax) were measured in all clinically relevant foci of increased FDG activity. In studies, showing multiple foci of increased FDG uptake the highest SUVmax value was recorded and used for further analysis.

**Statistical Analysis**

Comparison of SUVmax measurements of FDG uptake in sites of infection between different groups of patients was performed using the Mann-Whitney test. Differences with p<0.05 were considered statistically significant.

**RESULTS**

Between March 2010 and October 2015, a group of 217 patients underwent 243 PET/CT studies in search of a focal source of infection. After initial evaluation of their clinical records, 67 studies were excluded from further analysis including 23 studies in patients lacking information regarding administered antibiotics, 14 studies in patients with fever of unknown origin with a final non-infectious diagnosis and 30 studies with no further follow up.

The final study population included therefore 176 FDG PET/CT studies of 153 patients. There were 107 male and 46 female patients aged 18-86 years. Fifteen patients underwent multiple PET/CT studies. The reasons for performing FDG-PET/CT included suspected musculo-skeletal infection (n=70), vascular graft infection (n=39), bacteremia (n=31),
fever of unknown origin (n=30) and suspected polycystic kidney infection (n=6).

Elevated levels of C-reactive protein (a value above 5mg/l) and leukocytosis (higher than 12,000/µl) were found in 116 and 71 patients respectively. Fever (temperature above 38ºC) was measured in 64 patients with a mean duration of 5 days (1-38 days). A focal infectious process was diagnosed in 92 of the 153 patients (60%).

One hundred nineteen studies (68%) were performed in patients receiving antibiotic therapy for mean duration of 13 days (range 1-73 days) (Table 1). Antibiotics were administered intravenously in 63 patients, oral in 17 and as a combination of both in 39 patients. Fifty seven studies (32 %) were performed in patients who did not receive antibiotic treatment.

There were 124 positive (70%) PET/CT studies showing focal pathological FDG uptake. There were 107 TP cases including 63 studies (59%) in patients receiving appropriate antibiotic therapy (Figure1) for a mean duration of 11 days (range 2-32). Five of these TP patients received appropriate antimicrobial treatment for a duration of about a month (27-32 days). There were 44 TP studies in untreated patients including 27studies in untreated patients and 17 in those receiving inappropriate treatment (and thus considered as untreated), for a mean duration of 10.1 days, range 1-60, (Figure 2). The final diagnosis in the TP group included musculoskeletal (n=46), vascular graft (n=25) and post-surgical soft tissue (n=11) infection, abscesses in the kidney and lung (n=9 each) and abdomen (n=5), and central line infection and tuberculosis in one case each. In 67 of the 107 TP cases (63%) the final diagnosis was made by microbiology or/and pathology and in the remaining 40 cases by clinical and imaging follow-up for a period of 2- 24 months. There were 17 FP studies including 13 (76%) not receiving antimicrobial
therapy and 4 studies in treated patients. The final diagnosis in these FP studies was that of chronic granulomatotic or reactive post-surgical changes (n=7), an inflammatory soft tissue process (n= 3), and one case each of retroperitoneal fibrosis, Charcot osteoarthropathy, insufficiency fractures of pelvic bones, subcutaneous gluteal granuloma and physiological uptake in the aortic root. Two additional FP studies showed increased pericardial and vertebral FDG uptake of unclear etiology. Magnetic resonance imaging and clinical follow in these two cases up of 12 months did not reveal any pathology in these areas.

Fifty-two FDG PET/CT studies with no sites of pathological FDG uptake and no significant findings on imaging and clinical follow up of 2-24 months were defined as true negative. There were no FN results in the whole study population including the treated and the untreated patient groups.

SUVmax measurements at the TP sites of infection ranged from 1.6 to 17.9 (8.3±3.5) and in FP foci from 3.9 to 15 (7.5±3.2). SUVmax values in 63 TP studies performed in appropriately treated patients ranged from 1.6 to 17.9 (7.8±3.4), in 17 studies under inappropriate antibiotic treatment from 3.7 to 13.9 (8.2±3.3) and in 27 TP studies in patients who were not receiving antibiotic therapy from 4.0 to 16.7 (9.5±3.7). There was no statistically significant difference in the SUVmax measured in sites of infection between studies performed under appropriate antibiotic treatment and the untreated group (Table 2). Further analysis of SUVmax in sites of infection in patients receiving appropriate antibiotic therapy was performed according to the duration of treatment using
an arbitrary threshold of 6 days. There was no statistically significant difference in 
SUVmax measured in sites of infection treated for more or less than 6 days (Table 3).

**DISCUSSION**

FDG PET/CT plays a significant role in the assessment of various infectious processes 
such as osteomyelitis in the setting of a complicated diabetic foot (6,7), infected 
orthopedic (8,9) or vascular prostheses (10,11) and fever of unknown origin (12-14). 
Patients with suspected bacterial infection are frequently referred for FDG imaging while 
already receiving antibiotic treatment. Several investigators have questioned whether 
there are factors that can affect and specifically decrease FDG uptake in malignant and 
infectious processes. The effect of diabetes mellitus and hyperglycemia on the presence 
and intensity of FDG activity in malignant and infectious processes has been previously 
evaluated. The study showed that while hyperglycemia led to a higher FN rate in cancer 
patients it had, in contrast, no significant effect on the detectability rate of infectious 
processes. There was no statistically significant difference in the number of FN studies in 
this patient group (15).

The possible impact of antibiotic treatment on the diagnostic accuracy of FDG PET/CT 
in patients with suspected infectious processes has, to the best of our knowledge, not been 
previously investigated. In addition, no study has addressed the timing for performing 
FDG imaging in patients with infection in relationship to antibiotic treatment as well.

Present results in a large retrospective study of 153 patients demonstrate that FDG 
PET/CT correctly identified foci of increased uptake compatible with infection in more
than half of the study population, including all studies performed in patients receiving appropriate antibiotic therapy (59%) prior to imaging, with no FN results.

Of the 63 patients receiving appropriate therapy with true positive studies, five were treated for a long period of time of approximately one month. All these five cases had microbiological documented infections and the appropriateness of antibiotic treatment were based on the in vitro susceptibilities. The fact that their PET/CT studies were still positive after such a long duration of appropriate antimicrobial treatment is most probably due to the type, severity and/or location of their disease and the lack of response in spite of the appropriateness of the administered antibiotics.

In current study, SUVmax in sites of infection were slightly lower but with no statistically significant difference in patients who underwent FDG PET/CT while receiving appropriate antibiotic treatment in comparison to a group of untreated patients. The same results were obtained when comparing SUVmax in sites of infection in patients receiving appropriate antibiotic therapy divided into two groups according to the duration of treatment using an arbitrary threshold of 6 days. Scarce literature data in small series of patients have discussed the use of FDG imaging for antibiotic therapy control. In a study of 38 patients with spondylodiscitis the delta-SUVmax had a higher sensitivity for early identification of responders as compared to C-reactive protein levels (16). The response to antibiotic treatment was defined by a significant reduction in SUVmax between baseline and post-treatment PET/CT studies in a smaller group of 15 patients with infectious discitis (17). FDG PET/CT was also a useful tool in monitoring therapy
results in 25 patients with prosthetic vascular graft infections defining partial response as a decrease in SUVmax of more than 20% (18).

The fact that current study includes mainly single examinations in patients with no serial, longitudinal studies performed before and after antibiotic therapy does not allow confirming this previously published data showing the value of SUVmax changes in treatment monitoring. Further prospective well-designed studies are needed to determine whether serial SUVmax FDG measurements will be indeed able to demonstrate therapy control and define response to antibiotics in various infectious processes.

One relative limitation of this retrospective study may be related to the unavailability of follow-up data and information regarding administered antibiotics in 67 of the 243 studies. The fact that the study includes such a large number of patients underscores the significance of present results in spite of the relative heterogeneity of the study population including patients with a variety of clinical indications treated with different antibiotics regimens.

**CONCLUSION**

FDG-PET/CT accurately detected infection in more than half of our large study population including patients receiving appropriate antibiotic therapy prior to imaging, with no FN results. Antibiotic treatment appears to have no clinically significant impact on the diagnostic accuracy of FDG PET/CT performed for the assessment of known or suspected infectious processes.
ACKNOWLEDGMENT

No potential conflict of interest relevant to this article was reported.
REFERENCES


FIGURE 1. 53-year-old man, polycystic kidney disease, state after renal transplant, suspected infected renal cyst. The patient received appropriate antibiotic therapy for 11 days prior to the study. PET/CT images show increased FDG uptake surrounding a right renal cyst (arrows) consistent with infection. The patient continued antibiotic treatment with a clinical improvement but later underwent nephrectomy due to recurrent infection.
FIGURE 2. 62-year-old man, state after right femoro-popliteal bypass graft surgery, presented with a right groin soft tissue infection suspected to involve the vascular graft. The patient had received inappropriate antibiotic treatment for 4 days prior to the PET/CT study. FDG-MIP (A) and PET/CT images (B, C, D) demonstrate increased tracer uptake along the medial aspect of the right thigh involving soft tissues and the proximal part of the graft (arrows). The infected graft was removed and the diagnosis of infection was proven by pathology.
TABLE 1

Demographic and clinical characteristics of the study population

<table>
<thead>
<tr>
<th>Characteristic</th>
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<tbody>
<tr>
<td>Total no. patients</td>
<td>153</td>
</tr>
<tr>
<td>Age, range (years)</td>
<td>18-86</td>
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<tr>
<td>Gender (M/F)</td>
<td>107/46</td>
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<tr>
<td>Fever (no. patients)</td>
<td>64</td>
</tr>
<tr>
<td>Duration of fever (days, mean and range)</td>
<td>5 (1-38)</td>
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<tr>
<td>Impaired laboratory tests (no. patients)</td>
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<tr>
<td>Elevated C-reactive protein</td>
<td>116</td>
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<td>Leukocytosis</td>
<td>71</td>
</tr>
<tr>
<td>Total no. PET/CT studies</td>
<td>176</td>
</tr>
<tr>
<td>PET/CT studies in patients receiving antibiotic therapy</td>
<td>119 (70%)</td>
</tr>
<tr>
<td>Duration of treatment prior to PET/CT (days, mean and range)</td>
<td>13 (1-73)</td>
</tr>
</tbody>
</table>
TABLE 2

FDG SUVmax in foci of infection in 107 true positive studies according to antibiotic treatment. Comparison of SUVmax measurements in sites of infection between studies performed under appropriate antibiotic treatment and the untreated group (including patients receiving inappropriate therapy)*

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. studies</th>
<th>Duration of treatment , (days, mean and range)</th>
<th>SUVmax ( range, mean ±SD)</th>
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</thead>
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<tr>
<td>Appropriate</td>
<td>63</td>
<td>11(2-32)</td>
<td>1.6-17.9 (7.8±3.4)</td>
</tr>
<tr>
<td>Inappropriate</td>
<td>17</td>
<td>10 (1-60)</td>
<td>3.7-13.9 (8.2±3.3)</td>
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<tr>
<td>No treatment</td>
<td>27</td>
<td>___</td>
<td>4.0-16.9 (9.5±3.7)</td>
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</table>

* NS (not significant)
TABLE 3

FDG SUVmax in foci of infection in 63 true positive studies according to duration of appropriate antibiotic treatment.

<table>
<thead>
<tr>
<th>Appropriate antibiotic treatment</th>
<th>No studies</th>
<th>Duration of treatment (days, mean and range)</th>
<th>SUVmax, (range; mean±SD)</th>
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</thead>
<tbody>
<tr>
<td>≤ 6 days</td>
<td>20</td>
<td>4.3 (2-6)</td>
<td>1.6-12.8 (7.0±2.6)</td>
</tr>
<tr>
<td>≥ 7 days</td>
<td>43</td>
<td>14.4 (7-32)</td>
<td>2.8-17.9 (8.2±3.7)</td>
</tr>
</tbody>
</table>

N.S*  

* N.S. Statistically non-significant