The role of $[^{18}\text{F}]$fluoride positron emission tomography in the early detection of aseptic loosening of total knee arthroplasty


Department of Orthopaedic Surgery, University of Duisburg-Essen, Hufelandstr. 55, 45122 Essen, Germany
Department of Nuclear Medicine, University of Duisburg-Essen, Essen, Germany

KEYWORDS
F-PET; Total knee arthroplasty; Aseptic loosening; Prosthesis

Abstract
Total knee arthroplasty is successful in the treatment of degenerative, arthritic or injured joints. But the most important long term complication seems to be aseptic loosening. An inflammatory process at the bone/cement or bone/prosthesis interface leads to a severe osteolysis. Although early diagnosis is very important the standard techniques often fail. $[^{18}\text{F}]$Fluoride ion positron emission tomography (F-PET) is an appropriate tracer paired with a modern method for the evaluation of increased bone metabolism at the bone/prosthesis interface. In this preliminary study we describe for the first time the value of F-PET in the early diagnosis of aseptic loosening.

We studied 14 painful knee arthoplasties. In 6 cases the definite diagnosis was determined by surgical procedure, for 8 cases a long clinical follow-up of the least 6 months after the onset of symptoms led to the diagnosis. The F-PET scans were obtained by with an ECAT EXACT HR+ scanner with and without attenuation correction in the two- and three-dimensional mode. An intermediate or high uptake along the bone/prosthesis or bone/cement interface including either the tibial stem or the half of the femoral component was suspected to be aseptic loose. The result were compared with plain radiographs.

We found a sensitivity of 100%, a specificity of 56% and an accuracy of 71%. No false negative results were detected, in 4 patients one component as false positive. The sensitivity, specificity and accuracy for the plain radiograph of the same patients were 43%, 86% and 64%, respectively.

In conclusion PET seems to be a promising new method in the early diagnosis of painful TKA because of its excellent spatial solution. In combination with the bone

* Corresponding author.
E-mail address: thomas_sterner@yahoo.de (T. Sterner).

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Introduction

Total knee arthroplasty (TKA) has been performed with increasing frequency in the past few years. It improves the quality of life for many patients with degenerative, arthritic or injured joints. But a significant number of individuals suffer from pain some point after undergoing prosthetic joint implant surgery. Nowadays one of the most important long term complications is aseptic loosening of TKA. A chronic inflammation at the bone/prosthesis or cement/prosthesis interface is accused to be responsible for the aseptic loosening. Macrophages phagocytose wear particles at the interface, which initiate a chronic inflammation and leads to osteolysis and an increased osteoblastic and osteoclastic action. The earlier loosening is detected, the easier a surgical procedure can be performed. Before gross implant motion or osteolysis lead to definite radiographic changes, micro-motion and minor developments cause painful TKA, which cannot be easily detected by standard techniques. These techniques (laboratory tests, clinical parameters, plain radiography, bone scan, joint puncture) have a wide range in sensitivity (50–93%) and specificity (15–100%).

[18F]Fluoride PET gives the opportunity to measure quantitatively the bone metabolic activity. The first experience was made by Hawkins et al. in normal vertebrae. [18F]Fluoride is a bone-seeking tracer, which shows an increased uptake at high bone metabolism like the interface between bone and prosthesis in the case of aseptic loosening. Paired with positron emission tomography and its excellent spatial solution, this new technique is promising hints for detection of loose components of TKA.

In our preliminary study we want to evaluate the usefulness of [18F]fluoride PET in symptomatic TKA to detect early aseptic loosening. To our knowledge our study represents the first experience using [18F]fluoride PET to detect aseptic loosening of TKA.

Materials and methods

Patient population

In our population we had 14 patients with painful TKA, who were examined prospectively by means of F-PET between 2003 and 2004. There were six females and nine males with a mean age of 70.5 years (63.8–81.8 years). We studied a total of 14 knee prostheses (9 cemented, 3 cementless and 2 hybrid fixed knee prosthesis). The mean time between implantation and PET was 1.1–14 years (mean 3.1 years). Twelve patients had primary implants and two patients had already undergone revision arthroplasty. All revision operations were made by two experienced surgeons. In the absence of operative findings (n = 8) the final diagnosis was based on a long term clinical evaluation (at least 6 months). The F-PET findings were compared to conventional X-rays. All patients were volunteers and properly informed about the examination.

Diagnostic parameters

All patients underwent routine clinical examination, laboratory and radiological studies. For the laboratory studies, besides the routine parameters, we focused on the c-reactive protein, leucocytes and fibrinogen. We performed conventional X-rays of the symptomatic side in a.p. and lateral view and radiographs of the patella in 45° flexion. No clear diagnosis had been established in any patient before an F-PET scan was made. The definite diagnosis in six patients was found by revision surgery with intraoperative macroscopic, histological and microbiological findings. The histological and cultural specimens were taken from six different areas. For the femoral side specimens were taken from behind the femoral shield and of the lateral and medial condylus. On the tibial side we choose lateral and medial and in addition from the tip of the tibial stem. The histological specimens were sent in sterile containers to the Institute for Pathology of the University of Essen. They analysed the samples for signs of infection and aseptic loosening. The microbiological samples were immediately sent to the Institute of Medical Microbiology of the University of Essen. The results were given after long term (4 weeks) incubation.

[18F]Fluoride-PET imaging

PET imaging was performed with an ECAT EXACT HR+ scanner (Siemens Medical Systems), that
produces slices of 2.4 mm thickness with an axial field of view of 15.5 cm. \[^{18}\text{F}\]Fluoride was injected intravenously at a mean activity of 350 MBq. The first scans started 1 min after injection and were acquired in two-dimensional mode with at least two bed positions (range 2–4). The acquisition time for the emission was 2 min/bed position. Afterwards the transmission scan was performed (2 min/bed position). The second scans were done 60 min after injection in two- and three-dimensional mode. The acquisition time was 10 min/bed position, divided into 7 min emission and 3 min transmission. Then the same procedure was done for the two- and three-dimensional mode. The reconstruction algorithm was AW-OSEM with two iterations and eight subsets for the emission data. The data were stored in a 128 × 128 matrix.

**Image interpretation**

The scans were visually classified by two independent experienced nuclear medicine physicians. They were blinded to the clinical, biochemical and radiological findings. The only information they were given was the symptoms and the type of fixation (cemented/cementless). A consensus was reached on the basis of discussion.

The evaluation criteria based on the pattern and location of the \[^{18}\text{F}\]fluoride uptake at the prosthesis/bone interface or cement/bone interface in the case of cemented knee prosthesis. For the aseptic loosening we followed the criteria of Manthey et al.\(^\text{10}\) for TKA (Figs. 1–3). The visual analysis was preferred, because \[^{18}\text{F}\]fluoride uptake could differ within the same group.

Increased uptake in the prosthesis/bone interface, which includes the tibial stem or more than half of the femoral bone/prosthesis interface, was considered to be a sign of aseptic loosening. The \[^{18}\text{F}\]fluoride uptake showed a higher uptake than the contralateral side if carrying a prosthesis or the normal bone or soft tissue.

**Results**

The results of the individuals are listed in Tables 1 and 2. For six patients the diagnosis was confirmed by intraoperative, microbiological and histological findings. For eight patients a clinical follow up lasting at least 6 months confirmed the diagnosis. One patient with a loose femoral component quit the recommended operation.

The results were only valued as true negative or true positive if both components were correctly identified compared to the intraoperative finding or long clinical follow up (Tables 1 and 2).

F-PET correctly identified five of seven TKA as aseptic loose and this was confirmed by surgical treatment except for the patient mentioned above. In five out of seven cases we found no signs of aseptic loosening. In the clinical follow up (>6 months) the symptoms disappeared (Table 2). For four patients we found false positive results. In two patients PET diagnosed both components (femoral and tibial) as loose. During surgery just one component showed signs of aseptic loosening (Tables 1 and 2). The clinical follow up of the remaining two cases showed no clinical signs, although F-PET identified one component as loosened.

One patient was clinically classified as loose due to prolonged pain, although F-PET was negative (Fig. 3). The subsequent operative revision revealed that the PET diagnosis was correct, because no signs of loosening were detected.

In face of the few cases, we calculated the sensitivity, specificity and accuracy for aseptic loosening. We found a sensitivity of 100%,
a specificity of 56% and an accuracy of 71%. The sensitivity, specificity and accuracy for the plain radiographs of the same patients were 43%, 86% and 64% (Table 2).

In our study the final diagnosis was established without attenuation correction. We found no difference in the results by analysing non-attenuation corrected images compared to attenuation corrected images.

Discussion

Painful total knee arthroplasty is common and still a diagnostic challenge. Besides infection, which appears in 1.7–4.4%, aseptic loosening seems to be the main long term complication in modern prosthetics. The abrasion of the components leads to wear debris, which is phagocytosed by macrophages. Activated local macrophages release acute inflammation cytokines like TNFα or other bone metabolic proteins like OPG and RANKL. This mechanism leads to a stimulation of the local bone metabolism and osteolysis around the bone/prosthesis interface, which results in an aseptic loosening of the TKA. The plain radiograph often shows signs of loosening with a long time delay. Together with other standard methods like bone scan the literature reports a wide range of sensitivity (50–93%) and specificity (15–100%). But the earlier loosening is detected the easier is the surgical procedure and the greater the benefit for the patient.

Fluoride is a bone seeking tracer which shows an increased uptake in regions with high bone metabolism. Messa et al. proved the ability of the fluoride ion to measure bone metabolism quantitatively. In combination with the PET technique this method is more precise than using a γ-camera with bone seeking radiopharmaceuticals such as 99mTc-methylene diphosphonate because of the better resolution of the PET.

Studies describing F-PET concentrated on the measurement of bone metabolic activity in combination, e.g. with renal osteodystrophy.

Table 1 Patient information and results of the diagnostic procedure

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Prosthesis</th>
<th>Femoral component</th>
<th>Tibial component</th>
<th>Radiography</th>
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<tbody>
<tr>
<td>1</td>
<td>67</td>
<td>C</td>
<td>+</td>
<td>+</td>
<td>Fem+/Tib+</td>
</tr>
<tr>
<td>2</td>
<td>67</td>
<td>C</td>
<td>–</td>
<td>–</td>
<td>Fem−/Tib−</td>
</tr>
<tr>
<td>3</td>
<td>75</td>
<td>C</td>
<td>+</td>
<td>+</td>
<td>Fem+/Tib−</td>
</tr>
<tr>
<td>4</td>
<td>75</td>
<td>C</td>
<td>+</td>
<td>–</td>
<td>Fem−/Tib+</td>
</tr>
<tr>
<td>5</td>
<td>74</td>
<td>C</td>
<td>+</td>
<td>+</td>
<td>Fem−/Tib+</td>
</tr>
<tr>
<td>6</td>
<td>71</td>
<td>C</td>
<td>–</td>
<td>–</td>
<td>Fem−/Tib−</td>
</tr>
<tr>
<td>7</td>
<td>64</td>
<td>C</td>
<td>–</td>
<td>–</td>
<td>Fem−/Tib−</td>
</tr>
<tr>
<td>8</td>
<td>66</td>
<td>C</td>
<td>+</td>
<td>+</td>
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</tr>
<tr>
<td>9</td>
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<td>C</td>
<td>+</td>
<td>–</td>
<td>Fem+/Tib−</td>
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<td>10</td>
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<td>59</td>
<td>Nc</td>
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<td>Fem−/Tib−</td>
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<td>14</td>
<td>64</td>
<td>C</td>
<td>–</td>
<td>+</td>
<td>Fem−/Tib−</td>
</tr>
</tbody>
</table>

C, cemented; Nc, non-cemented; Fem, femoral component; Tib, tibial component; +, positive; −, negative.
osteoporosis, osteointegration of bone allografts, femoral head necrosis and malignant processes in the bone. Even-Sapir et al. describes that $[^{18}F] $fluoride PET is sensitive and specific for the detection of osteolytic bone lesions. At the bone/prosthesis or cement/prosthesis interface osteolytic bone lesions lead to aseptic loosening of one or both components. To our knowledge no studies have analysed the value of F-PET in this context. As mentioned above F-PET can be completed within 1 h and in combination with its excellent spatial resolution PET should be useful in the early detection of aseptic loosening.

In association with aseptic loosening of knee prosthesis recently a few studies were published using PET. The main topic of these investigations was the detection of infections. All groups used $[^{18}F] $fluorodeoxyglucose as tracer. FDG depends on the glucose uptake of the cells and does not represent the bone metabolism. This is the first study using a bone seeking tracer in combination with aseptic loosening.

An increased uptake of fluoride along the prosthesis interface including the stem of the tibial component or at least half of the femoral component was evaluated as loose (Figs. 1 and 2). Interestingly the intensity of uptake at the bone prosthesis interface was not so important as the pattern of the uptake (Figs. 1–3).

Using the above mentioned guidelines we found an excellent sensitivity (100%), but a low specificity of 56% (plain radiograph of the same group 86%).

In contrast to the sensitivity we found four patients with false positive results. An incorrect interpretation of the findings due to postsurgical findings is unlikely, because the interval between surgery and PET was over 1 year. Even a semiquantitative analysis using standardised uptake value (SUV) allows no benefit. Up to now we have no data of interference between the type of prosthesis and the results of PET along the bone/prosthesis or bone/cement interface. Zhuang et al. described the same problems in the interpretation of PET results in combination with TKA using FDG. Further research has to be done to define the factors which lead to the high rate of false positive results.

Unlike Goerres et al. who affirm in their phantom study measurements that attenuation correction produces artefacts, our results in vivo do not confirm these findings on a level of clinical significance.

Altogether F-PET seems to be a promising new technique for detection of aseptic loosening. Its excellent spatial resolution together with the bone-seeking tracer fluoride showed a very good sensitivity in detecting aseptic loosening. Overall our intention to detect aseptic loosening was fulfilled. But for reasons unknown the high rate of false positive results leads to a poor specificity. This study represents the first experience with F-PET with a small group of patients, but our results are promising. Further studies with larger series of patients are needed to solve the above mentioned problems and promote the role of F-PET. Furthermore, phantom measurements are needed to quantify interference between different types of TKA and the attenuation correction. All these issues are the subject of our current investigations.
References