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REVIEW ARTICLE

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Promising Role of 18-F-Fluoro-D-Deoxyglucose Positron Emission Tomography in Clinical Infectious Diseases

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Abstract 18-F-fluoro-D-deoxyglucose positron emission tomography (FDG PET) has become an established imaging tool in clinical oncology, cardiology and neurology and is now entering the field of clinical infectious diseases. The purpose of this article is to review the currently available, albeit limited, literature on FDG PET in the diagnosis of various infections and fever of unknown origin. Those indications for which FDG PET offers added value over more available techniques like labelled leucocyte scanning, gallium scanning and magnetic resonance imaging are especially highlighted. FDG PET seems to have an incremental value in the assessment of chronic osteomyelitis, especially in the axial skeleton, as well as in the diagnostic workup of fever of unknown origin and HIV complications. Cost-effectiveness studies are needed to define its place in the current diagnostic strategies of these pathologies.

Introduction

18-F-Fluoro-D-deoxyglucose (FDG) positron emission tomography (PET) has developed into an accepted tool in clinical imaging. Over the last decade its applications in clinical neurology, cardiology and especially in clinical oncology have increased considerably, paralleled by an increasing availability of PET cameras [1]. The ability to image glucose metabolism has proved to be the key to the current success of PET in different fields of medicine [2, 3, 4, 5, 6, 7]. FDG is currently the most commonly used PET tracer. Increased glucose metabolism is often present in tumours [8]. FDG PET is reported to be a sensitive and specific technique in oncological imaging [2, 3, 5, 6], but it is well known that inflammatory and infectious lesions can cause false-positive results [9]. Indeed FDG uptake is not specific for neoplastic cells. Autoradiographically, intratumoural FDG distribution in certain tumours is even highest in the reactive inflammatory tissue, i.e. the activated macrophages and leukocytes surrounding the neoplastic cells [10, 11].

In an experimental rat model of turpentine-induced inflammation, Yamada et al. [12] have shown that FDG uptake is high in inflammatory tissue and that uptake is higher in chronic than in acute inflammation. In another rat model of *Escherichia coli* infection, it has been demonstrated that FDG uptake is higher than that of other radiotracers such as 67-gallium, radiolabelled thymidine, methionine and human serum albumin [13]. Moreover, high target-to-background ratios are reached within the first hour after FDG injection, allowing for early imaging. It was shown autoradiographically that FDG uptake is highest in the area of inflammatory cell infiltration surrounding the necrotic region, especially in those regions with the highest number of macrophages and polymorphonuclear leukocytes [13].

In the early years of clinical FDG PET imaging in oncology, cases of false-positive uptake in a wide variety of infections were described [9]. What at first seemed a disadvantage has been exploited in a positive manner over the last years, resulting in a number of promising reports on the potential of FDG PET imaging in different types of infection and inflammation [14, 15, 16, 17].

The Tracer: 18-F-Fluoro-D-deoxyglucose

The tracer injected is the fluorinated glucose analogue. The mechanism of cellular uptake of FDG in tumoural cells has been described in detail [18]. Briefly, like glucose, FDG passes the cellular membrane and is phosphorylated by glucose 6-hexokinase. Glucose transmembranar transporter (GLUT) molecules as well as glucose 6-hexokinase activity are increased in malignant

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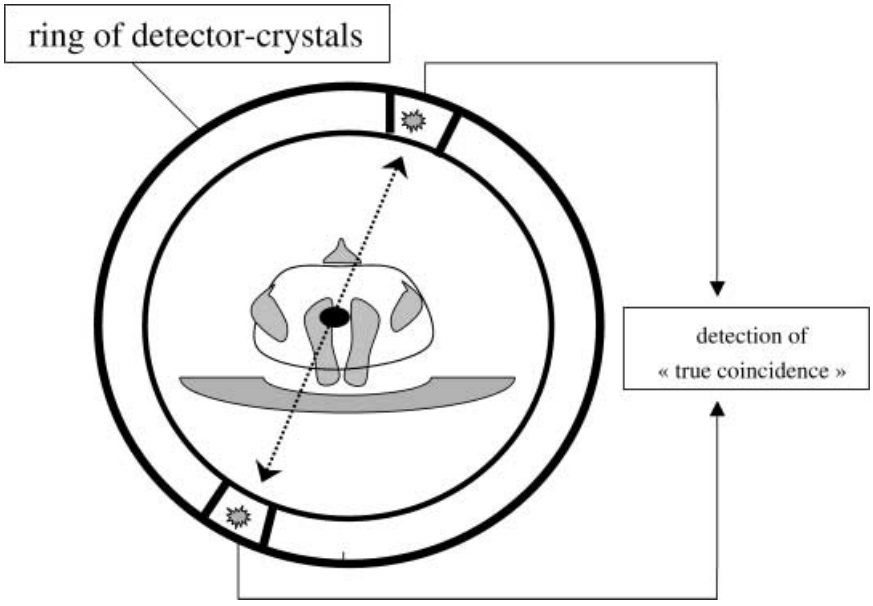

Fig. 1 Schematic presentation of the PET scanner and the "coincidence detection" process

cells. Phosphorylated glucose enters the glycolytic pathway for energy production. Phosphorylated FDG, however, is not further metabolized and remains trapped [2, 18]. Therefore, intracellular FDG concentration in tumours increases with time. The uptake mechanism in infectious and inflammatory diseases is currently not fully elucidated, but probably is related to the fact that granulocytes and macrophages use glucose as an energy source only during their metabolic burst [10, 11, 12, 19].

18-F-fluoride, the radioactive component bound to glucose, is a positron-emitting radionuclide and a cyclotron-produced product with a physical half-life of 110 min. It differs from conventional radionuclides (like 99m-technetium) because, after annihilation of a positron with a nearby electron, two 180° opposed gamma rays instead of one are emitted at the same time (Fig. 1).

To date, no side effects due to FDG injection have been reported. The patient dose is 0.027 mSv per MBq (milliSievert per megaBecquerel) administered, which is in the same magnitude of a computed tomography (CT) scan or a bone scan [20].

The Positron Emission Tomography Scanner and the Scanning Procedure

A dedicated PET scanner is composed of a ring of detector crystals. Only if the two high-energy (511 keV) gamma rays, emitted by the positron-emitting isotope (e.g. 18-fluoride), arrive at two 180°-opposed detectors of the ring detector within the same time window ("in coincidence") is a signal registered. The origin of the positron-emitting radionuclide is calculated from all data registered (Fig. 1). PET images are not qualitatively influenced by the presence of metallic implants. The main advantage of PET technology over conventional SPECT (single photon emission tomography) tracers (e.g. 99m-technetium) is that images with higher resolution can be generated, resulting in more anatomic information (±5 mm resolution for PET vs. 10–15 mm for conventional SPECT). Another advantage of PET over SPECT is that accurate determination of the amount of tracer in a lesion ("absolute quantification") is possible, which might be an advantage in objective (operator-independent) follow-up of therapy effectiveness.

A typical whole body examination can be performed in 45–60 min. Scanning times can be shortened if the area of interest is spatially more limited. During this glucose influx phase, physical activity has to be strictly minimized to prevent muscle uptake of the tracer. Patients are asked to remain sober at least 4 h before tracer injection. Glucose infusions should be replaced by saline solutions. False-negative findings due to elevated blood glucose concentrations, particularly those exceeding 11 mmol/l, are a well-known problem in FDG PET scanning in oncology [21]. Data concerning the importance of glucose levels on FDG PET in inflammation are scarce [22]. Until this relationship is clarified in larger series, we recommend stringent regulation of serum glucose concentrations, not to exceed 11 mmol/l, as is the current practice in oncological FDG PET [5].

The interpretation of FDG PET scans in infectious diseases has been described elsewhere and is usually straightforward. Briefly, a scan is considered positive when uptake is higher than the contralateral side or than adjacent tissues, taking into account the normal physiological uptake patterns [15].

We have summarized the advantages and disadvantages of FDG PET compared to conventional nuclear medicine techniques (i.e. three-phase bone scanning, leukocyte and gallium scintigraphy) and radiographic techniques (i.e. planar radiography, CT and MRI) in Tables 1 and 2, respectively.

Table 1 Advantages and disadvantages of FDG PET in infectious diseases compared to conventional nuclear medicine techniques

Advantages	Disadvantages
Early imaging (1 h), resulting in early reporting [13, 24]	Technique currently not widely available; high cost
High-resolution (±5 mm) tomographic images, allowing for differentiation between bone and soft tissue infection	Differentiation between tumour and infection or inflammation strictly not possible, though quantification might help [29]
High target-to-background ratio [13]	
Low bone, bone marrow and liver uptake	
Sensitive in chronic, low-grade infections [15, 25, 26]	
Highly accurate in the central skeleton [15, 25, 27]	
No additional scans necessary; all-in-one technique	
High interobserver agreement [15, 27]	
Patient dose 2–3 times lower when compared to gallium scanning [21, 28]	

Table 2 Advantages and disadvantages of FDG PET in infectious diseases compared to computed tomography and magnetic resonance imaging

Advantages	Disadvantages
Not hindered by metallic implants	Technique currently not widely available; high cost
Assessment of lesion activity: imaging of glucose metabolism is likely more specific than hyperperfusion or oedema (CT/MRI) [30]	Less anatomic information
Whole body screening	
No side effects	

CT/MRI, computed tomography/magnetic resonance imaging

Possible Indications for 18-Fluorodeoxyglucose Positron Emission Tomography in Infectious Diseases

FDG PET remains an expensive imaging modality when compared to conventional nuclear medicine procedures, planar radiographic techniques, computed tomography (CT) and magnetic resonance imaging (MRI). With increasing availability [1], cost will decrease in the next decade. Nevertheless, the introduction of FDG PET in the field of clinical infectious imaging is only justified if an added value compared to more available techniques can be shown, i.e. if patient management can be altered and if cost-effectiveness can be demonstrated. Indeed, even a very expensive diagnostic method like FDG PET can be cost-effective if it leads to more appropriate therapy. This has been already shown in an oncological setting [23].

We critically evaluated the limited literature available and have tried, on the basis of current evidence, to define a possible role for FDG PET in clinical infectious diseases.

Acute Osteomyelitis and Spondylodiscitis

Theoretically, FDG PET can be used for the diagnosis of acute osteomyelitis or spondylodiscitis, which is confirmed in experimental and clinical literature reports [13, 25, 28]. However, in the absence of complicating factors, the added value compared to the combination of physical examination, biochemical alterations in combination with three-phase bone scanning or especially MRI, is expected to be rather limited, as these techniques have high sensitivity (>90%) for this indication [31, 32, 33]. PET may have a role in rare doubtful cases, such as the differentiation between spondylodiscitis and erosive degenerative disk disease, where both MRI and bone scan may be falsely positive [17, 32, 34, 35, 36]. In these cases a negative PET will exclude infection [15, 25, 27].

Chronic Osteomyelitis

The diagnosis of chronic osteomyelitis is more complex. Any form of osteomyelitis can progress to a chronic state. Clinical symptoms persisting for more than 10 days correlate with the development of necrotic bone and chronic osteomyelitis [37]. Chronic osteomyelitis also includes the relapse of previously proven osteomyelitis. Although many techniques have been proposed for the noninvasive evaluation of chronic osteomyelitis, clinicians are still confronted with an indeterminate diagnosis in many patients and action is often limited to a “wait and see” policy or empirical antibiotic treatment [38, 39, 40]. Inflammatory parameters (C-reactive protein, erythrocyte sedimentation rate and leucocytes) lack sensitivity (especially in low-grade infections) and specifici-

ty [40, 41, 42, 43]. CT and MRI provide excellent anatomic detail. MRI is extremely helpful in unoperated cases but is currently of limited value in the presence of metallic implants as well as in discriminating between oedema and active infection after surgery [33, 44, 45, 46].

The use of three-phase bone scintigraphy in combination with leucocyte scan is generally accepted as a method with good clinical accuracy (79–100%) in the peripheral skeleton [31, 47, 48, 49, 50, 51]. The accuracy of this combined strategy decreases (i) in low-grade chronic infections [45, 47] (lower sensitivity); (ii) in the presence of periskeletal soft tissue infection due to the limited resolution of conventional nuclear imaging (lower sensitivity and specificity); (iii) in the central skeleton due to the presence of normal bone marrow and the possibility of so-called "cold lesions" (lower sensitivity and specificity) [15, 36, 47, 48, 50, 52]; and (iv) after trauma or surgery due to the presence of ectopic haematopoietic bone marrow (lower specificity) [49].

To prevent false-positive studies due to ectopic bone marrow, the combination of leucocyte scanning with bone marrow scanning (99m-technetium sulfur colloid) has been proposed. Congruency between leucocyte and bone marrow scanning indicates the presence of bone marrow, while a positive leucocyte scan without a congruent bone marrow image suggests the presence of infection [31]. In the vertebral column, a combination of bone and gallium scan has been proposed to improve both sensitivity and specificity [53]. However, the need for two or even three (bone scan/leucocyte scan/bone marrow scan or bone scan/gallium scan) techniques is not practical, adds to the cost and patient radiation dose and is time consuming. Therefore, an equally specific and sensitive all-in-one technique would be most welcome.

Guhlmann et al. [15] published the results of FDG PET and antigranulocyte antibody scintigraphy in 51 patients with suspected chronic osteomyelitis. Patients operated upon within the last 2 years were excluded. They found an excellent accuracy and interobserver agreement (reader1/reader2) for both techniques (97%/95% for FDG-PET and 86%/92% for antigranulocyte antibody scintigraphy; difference not statistically significant) in the peripheral skeleton (n=36). In the central skeleton (n=15), accuracy was significantly higher for FDG-PET (93%/100%) than for antigranulocyte antibody scintigraphy (73%/80%; P<0.05). In this prospective study, the presence or absence of infection was determined by surgical exploration in 31 patients and clinical follow-up in 20 patients.

Kälicke et al. [27] reported the results of FDG PET in 15 histologically confirmed cases of infection (8 with chronic osteomyelitis and 7 with acute osteomyelitis). FDG PET yielded 15 true-positive results. However, the absence of negative findings in this series may raise questions concerning selection criteria.

Similarly, we have reported our findings in 60 patients with a variety of suspected chronic orthopaedic infections [25]. Contrary to the study of Guhlmann et al. [15], patients with recent surgery were not excluded from this series. Considering only those with suspected chronic osteomyelitis, FDG PET was correct in 40 of 43 patients. There were three false-positive findings, 17 true-negative findings and no false-negative findings. This resulted in a sensitivity of 100%, a specificity of 85% and an accuracy of 93%. Two of three false-positive findings occurred in patients who had been operated recently (6 weeks and 4 months, respectively). In this prospective study, the presence or absence of infection was determined by surgical exploration in 15 patients and clinical follow-up in 28 patients.

Zhuang et al. [26] investigated 22 patients with suspected chronic osteomyelitis. FDG PET correctly diagnosed all six patients with chronic osteomyelitis. There were two false-positive findings, resulting in a sensitivity, specificity and accuracy of 100%, 87.5% and 91%, respectively. The two false-positive findings were caused by recent osteotomy. It is, however, not clear in this study for how many patients histopathologic or microbiologic studies were available.

Overall, the results published in this particularly difficult population are promising. PET images are not disturbed by the presence of metallic implants and are able to differentiate between scar tissue and active inflammation. These are major advantages compared to CT and MRI (Table 2).

FDG PET seems to be a very sensitive tool even for chronic and low-grade infections. FDG PET has an advantage over leucocyte scanning because small molecules like glucose are likely to penetrate easier and faster in lesions than cellular tracers or antibodies [54]. Taking into account published results and our own experience, a negative PET scan virtually rules out osteomyelitis [15, 25, 27]. Moreover, specificity seems to be high as well, especially if recently (less than 3–4 months) traumatized or operated bone is excluded [25, 26, 55]. Specificity is at least partly due to the superb imaging characteristics of PET cameras when compared to conventional nuclear medicine techniques, allowing discrimination between soft tissue and bone infection.

Although FDG PET has an excellent accuracy in the diagnosis of chronic osteomyelitis, it has been suggested that its use in chronic osteomyelitis is currently only warranted in the central skeleton since, for the peripheral skeleton, more available techniques like leucocyte scanning are adequate [15, 49]. Indeed, in one study comparing the combination of bone scan and leucocyte scan with FDG PET as a single technique, FDG PET was significantly more accurate in the central skeleton. For the peripheral skeleton, FDG PET results were better, but significance could not be reached [15]. Indeed, the usefulness of leucocyte scanning is low in the central skeleton due to the presence of normal bone marrow, which is also visualised on leucocyte scanning [52]. FDG shows very low uptake in normal bone marrow, allowing for easy detection of increased uptake (Fig. 2). Ideally, however, a prospective study between the combination of

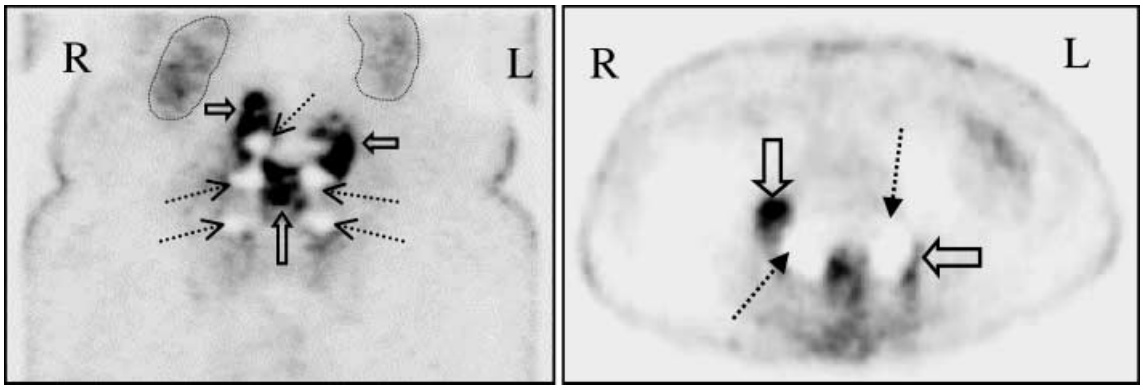

Fig. 2 A patient with lumbar osteosynthesis material and low back pain. In these circumstances, bone scan, leucocyte scan and MRI are not contributory. Coronal (left) and transaxial (right) FDG PET showed intense glucose metabolism (thick arrows) adjacent to the osteosynthesis material (dotted-line arrows). At surgery, a pus collection was found adjacent to the osteosynthetic implants

bone scan and gallium scan, currently the radionuclide gold standard for vertebral infections, and FDG PET should be performed. The first clinical results, the simplicity of the PET technique, the lower patient dose and the superior quality of the PET images when compared to tomographic bone and gallium scanning suggest an advantage for FDG PET.

An unexplored potential future use of FDG PET is the follow-up of suppressive antibiotic treatment. It remains to be proven whether FDG PET has an incremental value in this matter when compared to other, more available techniques. It can be argued that imaging activated inflammatory cells is more specific than imaging hyperaemia, as assessed by contrast-enhanced CT, MRI or three-phase bone scanning. Moreover, the ability of FDG PET to score uptake quantitatively (operator-independent; see above) might prove useful to monitor response to treatment and thus might have an impact on treatment decisions. This remains a hypothesis to be investigated.

Prosthetic Joint Infections

This is a particularly challenging field in which to date no simple diagnostic method is available [39]. Modern preventive measures have lowered the rate of infection to 0.5–2%, but given the large scale on which prostheses are implanted, this remains a large patient group [56]. Following revision arthroplasty however, the infection rate can exceed 30% [57, 58]. Due to the low incidence of infection in nonrevision prostheses, specificity of diagnostic techniques is crucial. Currently, radiographic methods and three-phase bone scanning are not able to differentiate between septic and aseptic loosening. The imaging gold standard (accuracy >90%) is considered to be the combination of leucocyte scan and sulfur colloid bone marrow scan, in which a dissociation in uptake pattern is diagnostic for infection [31]. However, leucocyte scanning is laborious, and thus expensive, and the labelling technique requires the manipulation of human blood. Scanning is ideally postponed until 24 h after injection. Moreover, in the case of a positive scan, additional bone marrow scanning is warranted to maintain specificity, adding to the complexity of the technique. Theoretically, FDG PET overcomes most of these problems, as the whole procedure could be performed safely in less than 2 h.

Recently, the value of FDG PET has been evaluated in 74 prostheses (36 knee and 38 hip prostheses) [59]. The respective sensitivity and specificity for detecting infection was 90.9% and 72% for knee prostheses and 90% and 89.3% for hip prostheses. In another study, however, Love et al. [60] found excellent sensitivity (100%) but low specificity (47%) for FDG PET (11 hip and 15 knee prostheses). Indeed, it is well known that the cell-rich vascular areas of the interface tissue between implant and bone and the pseudocapsule around aseptically loosened implants contain higher numbers of activated macrophages and proliferating fibroblast-like cells than the tissues around well-fixed implants [61, 62, 63, 64]. This may lead to increased FDG uptake. Consequently, FDG PET, though very sensitive, is probably not able to differentiate between aseptic loosening and septic loosening, as has been confirmed in other reports [65, 66]. Therefore, currently, it cannot be recommended in this clinical setting.

Fever of Unknown Origin

Fever of unknown origin (FUO) has been defined as recurrent fever of 38.3°C or higher lasting more than 3 weeks and remaining undiagnosed after appropriate in- or out-patient evaluation for a minimum of 3 days or three outpatient visits [67]. With modern diagnostic techniques available, the face of FUO has changed, with a relatively lower incidence of infections (20–25%) and neoplasms (around 10%) and proportionally more noninfectious inflammatory diseases (20–25%) observed compared to earlier studies [68, 69, 70] (Table 3).

From the point of view of medical imaging, the capability to perform whole-body screening is an important issue. The purpose of radionuclide imaging in patients

Table 3 Common causes of fever of unknown origin in which increased FDG uptake has been reported [68]

Pathology[a]
Neoplasms
Malignant
Hodgkin's and non-Hodgkin's disease [71]
Colon carcinoma [72]
Hepatoma [73, 74]
Renal cell carcinoma [75, 76, 77]
Sarcoma [78, 79, 80]
Eosinophilic granuloma [81]
Pheochromocytoma [82]
Benign
Atrial myxoma [83]
Renal angiomyolipoma [75]
Pheochromocytoma [75, 82]
Infections
Osteomyelitis, spondylodiscitis [15, 17, 25, 26, 27, 84]
Sinusitis [9]
Subphrenic abscess [17, 85]
Psittacosis [81]
Intravascular infection, vascular graft infection [17]
Infectious thrombophlebitis [17]
Tuberculosis [86, 87, 88, 89]
Fungal infections [90]
Pneumocystis carinii [87]
Infectious mononucleosis [91]
Adnexitis (pelvic inflammatory disease) [81]
Psoas abscess [17, 81]
Infected hematoma [17]
Miscellaneous [92, 93, 94, 95, 96, 97]
Multisystem disease (collagen/vascular/hypersensitivity disease)
Giant cell arteritis/polymyalgia rheumatica/aortitis [87, 98, 99, 100]
Rheumatoid arthritis [101, 102, 103, 104]
Takayasu aortitis [81, 105]
Granulomatous diseases
Inflammatory bowel disease [16]
Sarcoidosis [12, 14, 81, 106, 107]
Wegener's granulomatosis [87, 89]
Active lung fibrosis [81]
Miscellaneous
Inflammatory hematoma [87, 108]
Hyperthyroidism [10, 109]

with FUO is to localise a potential focus causing fever, which can subsequently be investigated by other diagnostic modalities. Whole-body leucocyte or murine monoclonal antigranulocyte antibody scintigraphy is not sensitive enough in FUO, because oncological pathology is not screened [47, 110, 111]. A "catch-all" tracer is needed for the diagnostic work-up of FUO [112]. Whole-body gallium scintigraphy is currently considered as the radionuclide investigation of first choice, because it images acute, chronic and granulomatous inflammation as well as various malignant diseases. In a large series of 145 patients investigated for FUO by whole-body gallium scintigraphy, gallium scanning contributed to the final diagnosis in 29% of the cases, a much higher yield than ultrasound (6%) or CT scanning (14%). On the basis of their findings, the use of gallium scintigraphy was suggested as a second-step (as opposed to a last-resort) procedure in the evaluation of FUO [69].

Whole-body FDG PET has several advantages over whole body-gallium imaging. Whole-body tomographic images are obtained within 60 min, with clearly superior image quality and resolution compared to whole-body tomographic gallium images. FDG has better tracer kinetics because the FDG molecule is much smaller than the relatively large 67-Ga transferrin complex, leading to higher lesion-to-background ratios at early time points [13]. Imaging can be started 1 h after injection of the tracer, allowing for rapid reporting [24]. Contrary to gallium scanning, there is low uptake of the FDG in the liver, the abdomen and the bone marrow, resulting in optimal imaging conditions. Moreover, the radiation dose to the patient is lower [21, 28].

Sugawara et al. [24] were the first to present their clinical findings in a variety of suspected infections in a small series. On the basis of the final clinical diagnosis, FDG-PET correctly identified the presence or absence of infection in 10 of 11 patients and missed one infectious focus due to suboptimal image quality in a diabetic patient with increased serum glucose levels.

Stumpe et al. [17] presented the results of 45 FDG PET scans in 39 patients with suspected infections. There were 40 true-positive findings, 4 false-positive findings and 1 false-negative finding, resulting in an overall sensitivity, specificity and accuracy of 98%, 75% and 91%, respectively. Though this was not a prospective comparison with CT or MRI, thus allowing bias, they found that CT was falsely negative in 3 of 15 scans and MRI in 4 of 24 scans. They concluded that FDG PET was clearly the most sensitive single examination. Because of the design of this study, a prospective comparison with CT and MRI is still warranted.

While the above reports have dealt with heterogeneous populations of patients with suspected infection, few papers have addressed the added value of FDG PET in the diagnosis of FUO. Blockmans et al. [113] prospectively studied 58 patients with FUO. In 20 (36%) patients, no final diagnosis was found. In 24 of 38 patients in whom a definitive diagnosis could be established, FDG PET contributed to the diagnosis (infection 6/10; cancer 3/6; multisystem disease 5/9; vasculitis 7/8, miscellaneous 3/3). In 40 patients, gallium scintigraphy was also performed. In this subgroup, FDG PET was contributory in 35% and gallium scanning in 25% (P=0.7). FDG PET was positive in all lesions that were positive on the gallium scan and seemed to be more sensitive in the diagnosis of vasculitis. The authors suggest that gallium scanning can be replaced by FDG PET, as the results are at least equivalent and because the results can be made available more rapidly (hours for FDG PET vs. days for gallium scintigraphy).

Meller et al. [81] compared the utility of FDG imaging and gallium-67 citrate tomographic imaging in patients referred for true FUO. All 20 patients underwent FDG imaging with a low-sensitivity PET system. In

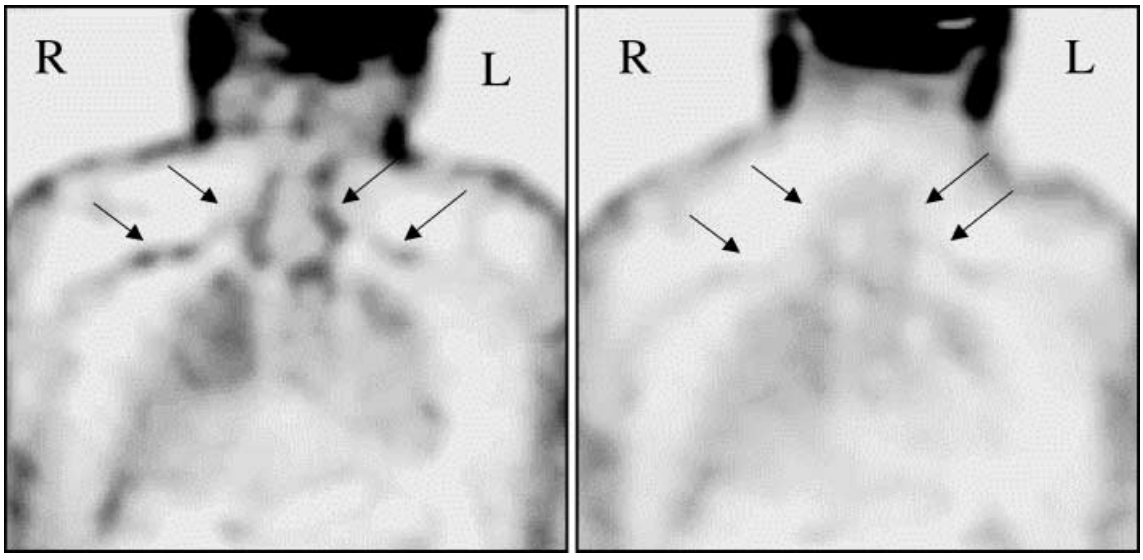

Fig. 3 A patient with fever of unknown origin. FDG PET coronal images (left) show increased FDG uptake in the large thoracic vessels and arteria carotis communis (arrows), suggesting arteritis. The arteria temporalis could not be visualized due to the proximity of the brain (high normal FDG uptake). Subsequently, arteria temporalis biopsy was performed, revealing giant cell arteritis. A follow-up scan (right) 6 weeks after initiation of corticoid therapy shows a decrease in the inflammatory process

18 patients, gallium planar and tomographic imaging (SPECT) was also available for comparison. The final diagnosis was infection in 8 of 20 (40%), autoimmune disease in 5 of 20 (25%) and neoplasms in 2 of 20 (10%). Fifteen percent (3/20) had other diseases. Fever remained unexplained in 2 of 20 (10%) patients. Though scanning was not performed on a PET scanner with optimal sensitivity, FDG imaging was positive and essentially contributed to the diagnosis in 11of 20 (55%) patients. When comparing FDG tomographic imaging directly with gallium tomographic imaging in the 18 patients, sensitivity and specificity in detecting the focus of fever were, respectively, 81% and 86% for FDG imaging and 67% and 78% for gallium SPECT.

Recently, Lorenzen et al. [87] reported the results of FDG PET in 16 patients with FUO. FDG PET was abnormal in 12 of 16 patients (infectious disease, 4; granulomatous/collagenous disease, 6; and cancer, 1; in 1 patient the PET results could not be confirmed by subsequent diagnostic work-up). Thus, FDG PET was found contributory in 11 of 16 (69%) patients. PET was negative in two patients with rheumatic fever. In the two remaining patients, no causative pathology was found.

On the basis of these three limited studies, it can be assumed that FDG PET has an added value to conventional screening in 40–70% of the patients with true FUO. Though a prospective comparison in a large series to date has not been published, this is higher than the 29% found by Knockaert et al. [69] for gallium scanning.

As shown in Table 3, FDG PET not only images neoplastic or infectious lesions but is also able to visualize multisystem diseases like Takayasu aortitis, giant cell arteritis or even rheumatoid arthritis (see also Fig. 3).

In conclusion, FDG PET, when available, seems to be preferable to gallium scintigraphy in the diagnostic work-up of patients with FUO. A cost-effectiveness study comparing an FDG-PET-based strategy (second-step) versus a conventional strategy, eventually followed by third-line FDG PET, is warranted.

AIDS

We have considered the problem of FUO in human immunodeficiency virus (HIV) infection as a separate clinical entity, as the frequency distribution of etiologic disease is quite different. HIV-infected patients may at a certain time develop symptoms of fever, weight loss or deterioration of mental function, which classifies them as having the acquired immunodeficiency syndrome (AIDS) [114]. Many pathologies, mostly neoplastic and/or infectious, may be underlying. Often, clinical examination, chest radiograph, haematological and biochemical analyses and blood and urine cultures reveal the causative pathology. However, additional imaging remains necessary in a number of cases to guide further diagnostic work-up. Especially when thoracic pathology is suspected, gallium scanning has proven useful [53]. The use of gallium scanning, however, poses several problems on top of the disadvantages that have been discussed above. Evaluation of brain and abdomen are difficult, and the appearance of persistent generalized lymphadenopathy and lymphoma may be similar. Moreover, compared to FDG imaging, the time to complete a study (24–96 h) is much longer [28].

Hoffman et al. [115] were the first to describe the use of FDG PET in HIV-infected patients. CT and MRI cannot differentiate between lymphoma and toxoplasmosis. The two diseases, however, differ in treatment and prognosis. Eleven patients with AIDS and central nervous system lesions on CT or MRI scans were studied with

FDG PET. On the basis of a semiquantitative scoring system (optimal cut-off value for FDG uptake), FDG PET accurately differentiated between lymphoma (*n*=5) and nonmalignant pathology (toxoplasmosis, *n*=4; syphilis, *n*=1; progressive multifocal leucoencephalopathy, *n*=1) in all patients. FDG uptake was significantly higher in the lymphomatous lesions than in the nonmalignant lesions.

O'Doherty et al. [116] investigated the utility of FDG PET in 80 HIV-infected patients with fever, confusion or weight loss and without clinical evidence of *Pneumocystis carinii* infection. In 23 of them, on the basis of a ring-enhancing lesion on MRI scan, FDG brain PET was performed. Six of them proved to have lymphoma, and all of them showed increased FDG uptake (sensitivity and specificity, 100%). Thirteen patients had toxoplasmosis and three had progressive multifocal leucoencephalopathy, but FDG uptake in these lesions was significantly lower, allowing for differentiation. The remaining 57 patients were investigated by half-body PET (from vertex to mid-thigh). In 25 patients, moderate (*n*=5) or high (*n*=20) uptake was found. Twenty-three true-positive results were obtained. The two false-positive results were due to persistent generalised lymphadenopathy (*n*=15; 13/15 true negative). There were two false-negative results (Kaposi's sarcoma of the lung; *n*=2). The overall sensitivity of half-body FDG PET for pathology needing therapy was 92% (23/25), while specificity was 94% (30/32).

Using FDG PET in 47 AIDS patients, Santiago et al. [117] found a lesion sensitivity of 82.5% for FDG imaging. Specificity could not be determined as not all patients in whom FDG imaging was positive had a definite diagnosis. In proven lesions, FDG imaging was more sensitive than gallium imaging in a subgroup of 28 patients (87/100 lesions detected with FDG imaging and 61/100 lesions detected with gallium imaging; *P*=0.051). The lower sensitivity in this series compared to the series of O'Doherty et al. [116] could be explained by the use of a low-sensitivity PET system (so-called "coincidence camera"), which is qualitatively inferior to currently available modern dedicated PET systems. It is a well-known problem in oncology that such systems have difficulties detecting lesions smaller than 1.5 cm [118].

In conclusion, FDG PET seems to be a promising tool in the work-up of HIV complications. Cost-effectiveness studies are needed to justify its use as a second-line strategy.

Conclusions

Promising results have been obtained with FDG PET in the field of clinical infectious diseases. In general, the specificity of FDG PET will be limited by the fact that FDG accumulates in sterile inflammatory lesions and tumours. Depending on the clinical setting, this may restrict the use of FDG PET in infectious diseases or may be irrelevant. In most patients, medical history makes the presence of tumour unlikely, and sterile inflammations such as chronic polyarthritis, vasculitis and tumours often appear at sites or show distribution patterns that are suggestive of these diseases. Moreover, it can be argued that FDG uptake is more specific than hyperaemia, as assessed by contrast-enhanced dynamic CT and MRI or three-phase bone scanning.

Several indications are especially promising:

(i) chronic osteomyelitis, especially in the central, bone-marrow-containing skeleton. The presence of metallic implants poses no problems for diagnosis. An interval of 3–6 months post surgery should be allowed to prevent false-positive findings. For the moment, there are not enough arguments to recommend the technique in the assessment of infection in joint prostheses.
(ii) fever of unknown origin, where it seems to be preferable over gallium scanning; and
(iii) AIDS, especially for the differential diagnosis of central nervous system lesions and for the early detection of complications. Cost-benefit studies and larger series are needed to implement FDG PET in the current diagnostic strategies.

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