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Review Article

Growing applications of FDG PET-CT imaging in non-oncologic conditions

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Abstract

As the number of clinical applications of 2-[fluorine 18]fluoro-2-deoxy-D-glucose (FDG) positron emission tomography/computed tomography (PET-CT) grows, familiarity with the conditions that can be diagnosed by this modality and when relevant pieces of additional information can be obtained becomes increasingly important for both requesting physicians and nuclear medicine physicians or radiologists who interpret the findings. Apart from its heavy use in clinical oncology, FDG PET-CT is widely used in a variety of non-oncologic conditions interconnecting to such disciplines as general internal medicine, infectious diseases, cardiology, neurology, surgery, traumatology, orthopedics, pediatrics, endocrinology, rheumatology, psychiatry, neuropsychology, and cognitive neuroscience. The aim of this review was to summarize the current evidence of FDG PET-CT applications in evaluating non-oncologic pathologies and the relevant information it can add to achieve a final diagnosis.

Keywords: 18F-fluorodeoxyglucose (FDG), positron emission tomography (PET), computed tomography (CT), non-oncologic, inflammation, infection

Introduction

The clinical applications of positron emission tomography/computed tomography (PET-CT) with the glucose analogue 2-[fluorine 18]fluoro-2-deoxy-D-glucose (FDG) are spreading beyond the area of oncology. Apart from concentrating in malignant tissues, FDG is also accumulating at the sites of infection and inflammation due to increased glycolytic activity of inflammatory cells such as neutrophils, lymphocytes, and macrophages. This increased FDG uptake is based on the fact that these cells use glucose as an energy source only after activation during the metabolic burst[1–2]. For instance, mononuclear cells and granulocytes use large quantities of glucose by way of the hexose monophosphate shunt and their rates of oxygen uptake increase intensely during their so called "respiratory burst" while fighting an infection[2]. When stimulated by phagocytosis,

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the hexose monophosphate shunt increases up to 20-30 times the baseline value, being the cause of high FDG uptake[3]. The involved mechanisms have been commonly linked to increased intracellular hexokinase and phosphofructokinase levels as well as increased numbers of cell surface glucose transporter proteins such as GLUT 1[3–5]. For example, it has been shown that stimulation with cytokines results in GLUT 1 overexpression and increased glucose uptake in both inflammatory and granulation tissues[6]. This avidity of inflammatory cells for 18F-FDG has led to the concept of using FDG PET-CT for imaging a variety of inflammatory and infectious conditions, including granulomatous diseases and fungal infections. Furthermore, *ex vivo* labeling of white blood cells with FDG represents an initial attempt to develop an infection-specific positron emitting tracer[7–8].

In the heart, FDG uptake by the myocardium allows assessment of myocardial viability in patients with myocardial ischemia, revealing potential regions of hibernating but viable myocardium. As a matter of fact, in many centers, cardiac FDG PET is becoming the gold standard for assessment of myocardial viability. In patients with cardiac sarcoidosis, FDG PET has proven useful as a follow-up tool for disease monitoring[9]. Of note is that a high percentage of cardiac sarcoidosis patients have arrhythmias and implanted cardiac devices that may interfere with a cardiac MR examination.

In the brain, FDG uptake by the cortical and subcortical structures allows noninvasive quantification of cerebral metabolism and may provide valuable information before any morphological changes become discernible. Current evidence in patients with epilepsy indicates that FDG PET may provide crucial data that guide surgical resections of the epileptogenic zone for medically refractory epilepsy[10]. A decade of brain PET research has also provided evidence that brain FDG PET is an effective and safe modality to identify diagnostic patterns of glucose hypometabolism in neurodegenerative dementias and is an effective and useful adjunct to other diagnostic information in the assessment of patients with progressive cognitive impairment[11]. Potential new areas that require further investigations may extend to evaluating the functional integrity of the brain in a variety of conditions like fetal alcohol spectrum disorders, especially becaus such functional abnormalities have already been reported by SPECT[12].

Hereby, we aimed to provide a concise summary of the broad areas of FDG PET-CT applications in non-oncologic conditions.

FDG PET-CT for diagnosis and treatment monitoring of inflammatory and infectious diseases

Tissue inflammation results in increased FDG accumulation, making the methodology useful for detecting a variety of chronic or occult infections. It is not uncommon for the site of infection or inflammation to have elevated FDG activity, but unremarkable anatomical changes. An increasing number of reports indicate that FDG PET-CT has become a useful tool in the diagnosis, treatment evaluation and follow-up of patients with such conditions as sarcoidosis, spondylodiscitis, and vasculitis, and is already the gold standard for some indications[1,13–14]. An example of FDG-avid tracheobronchitis without obvious CT findings is provided in ***Fig. 1***. For other diseases, such as inflammatory bowel diseases, rheumatoid arthritis, autoimmune pancreatitis, and fungal infections, hard

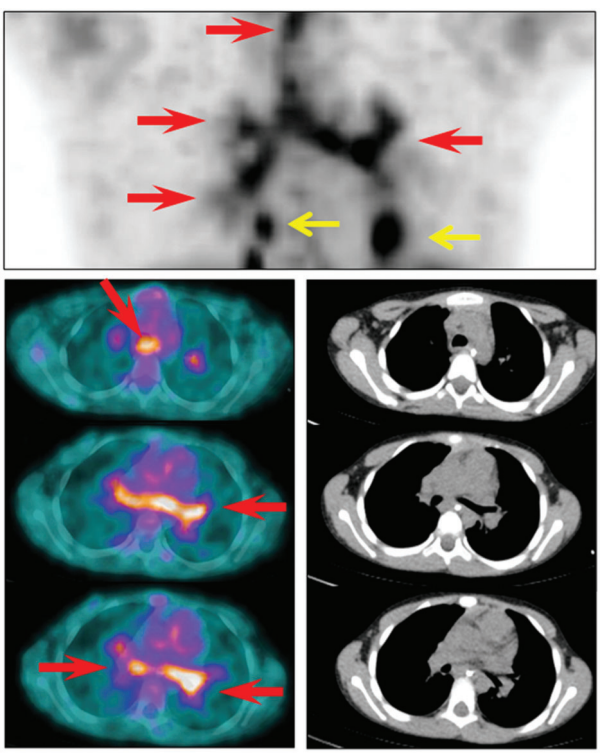

***Fig. 1* FDG PET-CT findings in a patient with tracheobronchitis.** The patient reported severe coughing for 2 years. PET images demonstrated intense FDG activity throughout the tracheal and bronchial walls (red arrows), consistent with tracheopbronchitis. No obvious tracheal or bronchial wall thickening was apparent on CT. Several foci of increased FDG activity in the lungs (small yellow arrows) were indicative of associated inflammatory changes in the adjacent lung parenchyma, even though the parenchimal lesions could not account for patient's persistent cough.

evidence is lacking, but studies also point out that FDG PET-CT could be useful[1].

FDG PET is a promising technique in detecting acute and chronic infection in the axial and peripheral skeleton. Precise location of osteomyelitis is vital for early therapeutic interventions. FDG PET has been reported to have an excellent sensitivity, normally reaching or exceeding 95%, with high specificities above 87%[15–16]. The modality proved especially valuable in patients with chronic osteomyelitis or suspected recurrence. In most cases, osteomyelitis is limited to a specific bone or body area, making it suitable for magnetic resonance imaging (MRI), which is also highly accurate for detecting bone infections without exposing the patient to any radiation. In clinical practice, however, different factors may need to be considered, including associated conditions, equivocal imaging findings, MRI contraindications or claustrophobia. Osteomyelitis in children, for example, can present with disseminated foci involving several bones, with a higher chance of being detected using a whole body imaging modality such as FDG PET or whole body MRI. In patients with diabetes mellitus, on the other hand, peripheral insulin resistance and diabetic microangiopathy might also translate into lower FDG uptake at the site of inflammation. Comparative studies performed in patients with non-healing diabetic foot ulcers indicate that MRI appears superior to FDG PET in detecting foot ulcer-associated osteomyelitis and might be the preferred imaging modality in such cases[17]. Despite these limitations, FDG PET still can play a valuable role in the setting of Charcot's neuroarthropathy by reliably differentiating it from osteomyelitis, both in general and when foot ulcer is present[18]. Furthermore, studies performed in patients undergoing surgical interventions report that the differentiation between Charcot's lesions and florid osteomyelitis provides the surgeon with important additional information, which is often unavailable from MRI. Because of this important additional data, PET could be considered preferable to morphologic imaging (CT, projection radiography) in the preoperative work-up of Charcot's foot[19].

The FDG uptake patterns may also help differentiate between inflammatory and degenerative changes in the vertebral body endplates and predict or exclude spondylodiscitis[20]. Due to its high sensitivity, a negative PET result in the setting of a diagnostically unclear case diminishes the need for surgical intervention. In contrast, a positive PET result does not always clearly establish the cause of increased FDG uptake and may require further investigations[20]. At the moment, the competition between MRI and FDG PET-CT for the detection of osteomyelitis, spondylitis or spondylodiscitis is still ongoing and new prospective controlled clinical trials have to be performed to answer the question of which imaging modality is most efficient for such patients[15].

FDG PET has also been reported as a useful imaging modality for detecting infections associated with lower limb arthroplasty. Comparative studies showed a relatively higher accuracy for detecting infections associated with hip prostheses (sensitivity, specificity, and accuracy of 90%, 89.3%, and 89.5%, respectively) versus those associated with knee prostheses (sensitivity, specificity, and accuracy of 90.9%, 72.0%, and 77.8%, respectively)[21]. In the literature, there are two predominant opinions related to the patterns of FDG uptake in septic and aseptic loosening of hip prostheses[22]. The first opinion suggests that septic and aseptic loosening are not characterized by a specific topographic pattern of FDG distribution, the differentiation relying on the quantity of FDG uptake with higher values in septic loosening[22–23]. However, it is known that intense FDG activity can exist in the head or neck portion decades after hip arthroplasty in asymptomatic patients[24]. The second opinion hypothesizes that FDG localization in bone-prosthesis interface is a characteristic of septic loosening. Thus, when FDG PET is used to diagnose periprosthetic

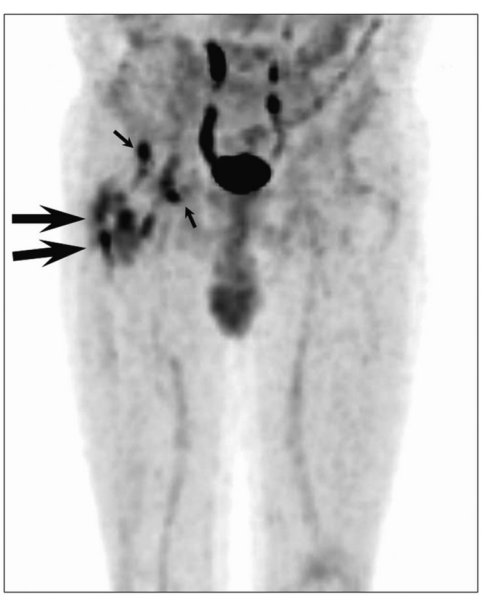

Fig. 2 **FDG PET findings in a patient with infected right hip prosthesis.** The patient presented with persistent pain in his right hip despite receiving prior courses of empiric antimicrobial therapy. Elevated FDG activity in the prosthesis head region at the bone-prosthesis interface (small arrows) may be nonspecific; however, distal activity in the prosthesis shaft (large arrows) is consistent with focal infection.

infection in patients with hip arthroplasty, the location of increased FDG uptake appears more important than the intensity of the uptake[25]. Therefore the presence of an osteolytic area seen on X-ray with little or absent FDG uptake on PET should be related to aseptic loosening[21–22,24–25]. In contrast, a negative PET result in the setting of a diagnostically unclear situation eliminates the need for revision surgery due to the high sensitivity of PET[26]. ***Fig. 2*** illustrates a patient with an infected right hip prosthesis. While the elevated activity in the prosthesis head, i.e. bone-prosthesis interface, may be non-specific, distal activity in the prosthesis shaft provides a valuable diagnostic clue.

FDG PET-CT is a reliable modality for the diagnosis of vascular graft-related infection. The precise anatomic localization of increased FDG uptake enables accurate differentiation between graft and soft-tissue infection as well as identification of potentially lethal complications such as fistulas into adjacent structures[27–29]. Studies performed in patients with "non-acute" vascular prosthesis infection showed that FDG PET-CT gave reliable results with an accuracy over 95% in 75% of prostheses and an accuracy of 70%–75% in the remaining 25% of cases[29].

Excessive FDG uptake in blood vessel walls can be also seen in such conditions as central and peripheral vasculitis (***Fig. 3*** and ***4***), associated intravascular thrombosis (***Fig. 5***) or other blood vessel abnormalities. Since no other imaging method is able to directly detect acute inflammation within the aortic wall, FDG PET has been demonstrated to be a powerful tool in evaluating patients with pathologies such as aortitis or giant cell arteritis. It can be also used to follow the development of vasculitis activity during therapy

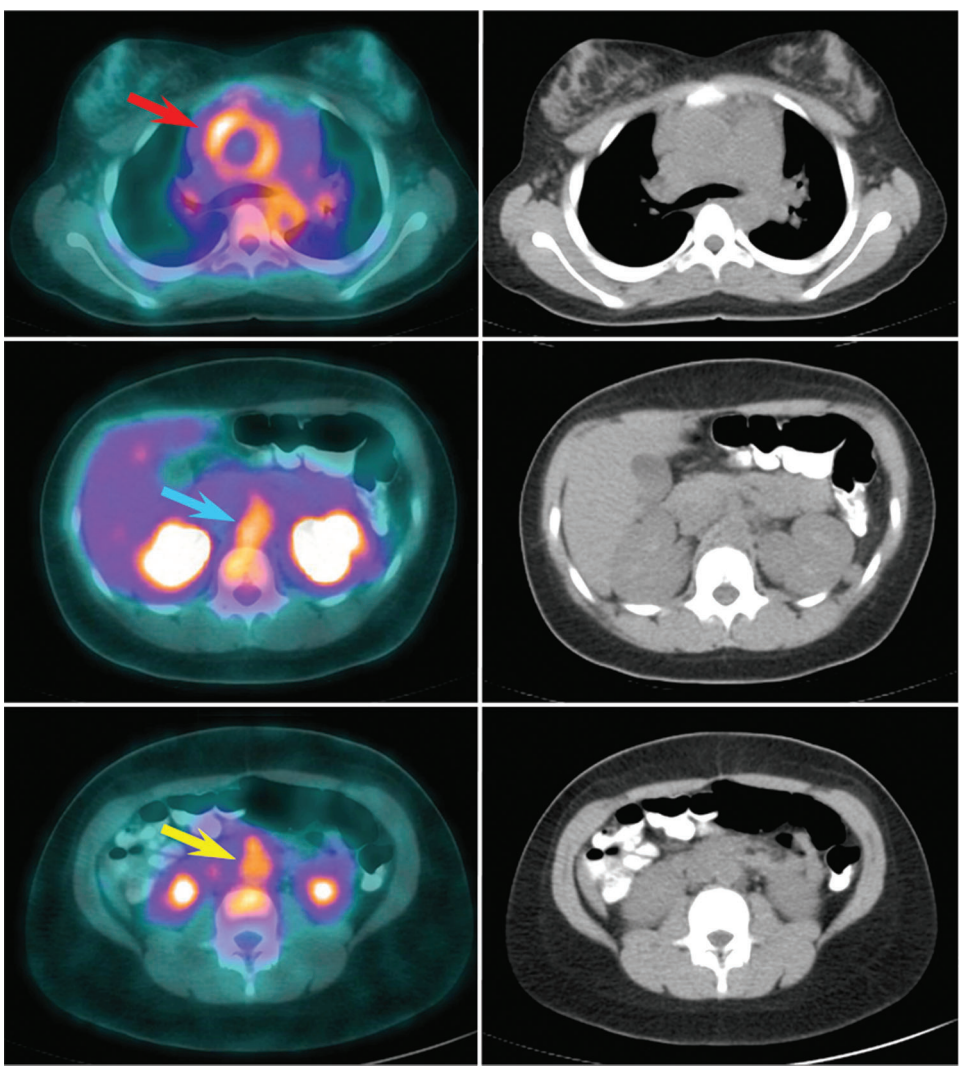

Fig. 3 **FDG PET-CT images of a patient with biopsy proven arteritis.** Elevated FDG activity can be seen in the arterial wall of the aortic root (arrow red, upper panel), celiac artery (arrow blue, middle panel) and superior mesenteric artery (arrow yellow, lower panel). Left panels display fused PET-CT images, while right panels show corresponding CT slices.

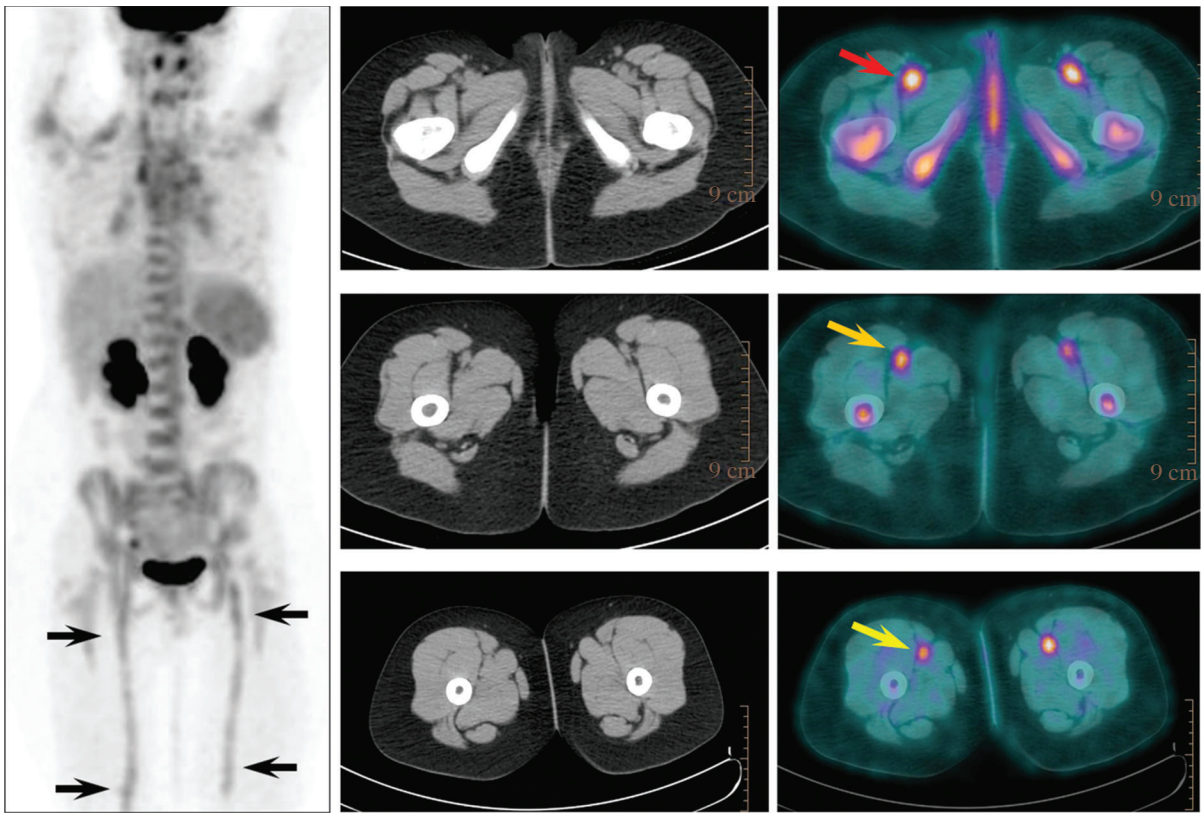

Fig. 4 **FDG PET-CT images of a teenager with fever of unknown origin.** Linear FDG activity in both legs seen on maximum intensity projection (MIP) images (black arrows, left panel) localized to proximal (red arrow), middle (orange arrow) and distal (yellow arrow) femoral arteries on fussed PET-CT images (right panel). Arteritis was subsequently confirmed as the cause of his fever of unknown origin.

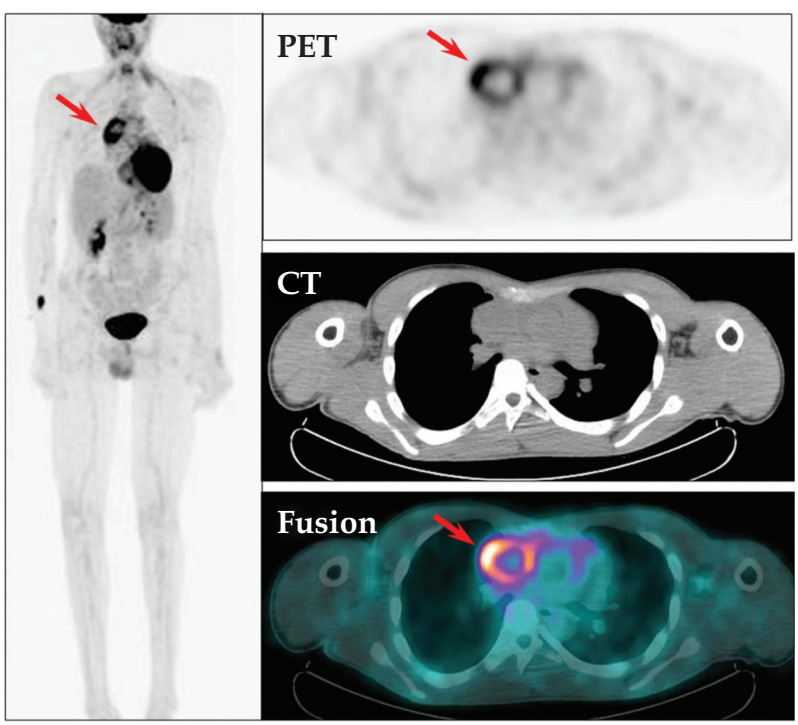

Fig. 5 **FDG PET-CT images of a patient with superior vena cava thrombosis.** Intense FDG activity is seen at the periphery of the thrombus as pointed by arrows. Associated dilation of the superior vena cava in this region is also apparent on CT.

as well as to delineate which vessels are involved[30–31]. Studies aimed to semiquantify the relationship between aortic and liver uptake in patients with giant cell arteritis showed that FDG PET region-of-interest analysis with aorta-to-liver maximal standardized uptake value ratios is a reliable, investigator-independent indicator of large-vessel inflammation. Receiver operating characteristic (ROC) analysis revealed optimal selectivity for a cut off ratio of 1.0, which was associated with a sensitivity of 88.9%, a specificity of 95.1%, and an accuracy of 94.4%[30]. Vasculitis represents a relative rare PET indication and the assessment with FDG PET remains difficult and dependent on the experience of the investigator[30]. The use of FDG PET in a variety of other systemic diseases and infections is also expanding. For example, Wegener granulomatosis lesions could be detected earlier by FDG PET-CT than by serum PR3-ANCA titers[32]. The modality proved also feasible for determining the biopsy sites, evaluating lesion activities, therapeutic monitoring, and follow-up of Wegener granulomatosis[33]. In patients with dermatomyositis or paraneoplastic syndromes and associated malignancies, FDG PET-CT imaging may offer an ''all-in-one'' procedure as an alternative to other diagnostic procedures, reducing the number of unnecessary investigations[34]. Associated infections in oncologic patients undergoing FDT PET-CT imaging also require differentiation from neoplastic lesions. Multiple studies have shown that dual time-point imaging of FDG PET may be helpful in differentiating malignancy from benign processes, including associated infections[35,36]. However, exceptions exist and new developments are required to further define the roles of FDG PET-CT in the management of infections in patients with associated malignancies[37].

In subjects with sarcoidosis, FDG PET-CT is more sensitive than the Gallium scan[38], which was traditionally used in the evaluation of sarcoidosis. It allows obtainment of a complete morpho-functional cartography of inflammatory active localizations and follow-up treatment efficacy, particularly in atypical, complex, and multisystemic forms[39]. The concurrent presence of FDG-avid lymphadenopathy and the ''scar sign'' (a rare but characteristic cutaneous manifestation of sarcoidosis) is a useful finding on FDG PET-CT to suggest sarcoidosis, especially when biopsy specimens are difficult to obtain[40–41]. Apart from evaluating the extent of disease, FDG PET-CT can uncover a suitable location for biopsy in such patients. Furthermore, the detection of unexpected organ involvement may offer prognostic value[42]. Studies investigating the presence of bone/bone marrow localizations of sarcoidosis showed that more than one-third of PET-CT-positive sarcoidosis patients had osseous abnormalities on PET-CT and the majority of these lesions (94%) could not be detected on low-dose CT[43].

Usefulness of FDG PET-CT in other granulomatous diseases such as tuberculosis has also been described, where the modality has the advantage of being able to screen the whole body and can assist in preventing unfavorable clinical results based on misdiagnoses[44–46]. Additionally, FDG PET-CT allows an easy evaluation of early therapeutic response in patients with tuberculosis, particularly those presenting with extra-pulmonary disease[47]. The technique also enables the differentiation between patients with active granulomatous inflammation and those with fibrous lesions. In many patients, however, the FDG avid lesions are rather not specific, and the differentiation of extrathoracic lymphadenopathy from metastatic disease or lymphoma may be difficult. Therefore, familiarity with the functional imaging features of granulomatous inflammatory lesions in various anatomical locations plays a crucial role in the diagnosis and management of these patients[48].

FDG PET-CT in patients with HIV

In patients with HIV infection, resting lymphocytes are activated and switch to glycolysis, increasing their glucose uptake by around 20-fold over 24 hours[49]. This increased glucose utilization by activated lymphocytes can translate into increased FDG uptake in the affected lymph nodes[49–50]. Studies performed in HIV-infected patients reported that FDG uptake was a sensitive marker of disease state and its relation with $CD8^+/CD38^+/CD45RO^+$ T cells indicates that it can be considered a marker of disease status[51]. Whole-body FDG PET images have even shown a specific pattern reflecting the HIV stage, suggesting that lymphoid tissues are engaged in a predictable sequence[52]. Such patterns include increased FDG uptake in the head and neck during the acute phase (a), FDG avid cervical, axillary, and inguinal lymph nodes during the mid stages (b) and increased FDG accumulation in the colon with associated FDG avid mesenteric and ileocecal lymphadenopathy during the late disease stages (c)[49,52]. While this may provide valuable information related to the anatomic correlates of HIV progression without the need for biopsy, care should be taken as it can also lead to false-positive interpretations of malignancy.

FDG PET-CT proved valuable in detecting both infections and malignancies in HIV-positive patients, showing an overall sensitivity and specificity of over 90% for localization of focal pathology in subjects presenting with unexplained fever, weight loss, or

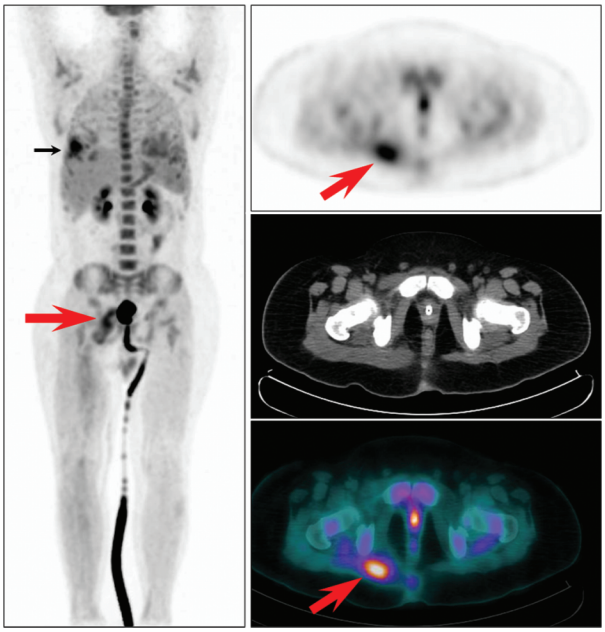

***Fig. 6* FDG PET-CT findings in a patient with fever of unknown origin.** The investigation revealed an unsuspected abscess in the right gluteus muscle (large arrows red) and a second FDG-avid focus in the right lung (small black arrow).

confusion[53]. The modality has also the ability to differentiate malignancy from infectious lesions in the central nervous system of patients with HIV infection, guiding the initiation of the appropriate treatment and precluding the need for invasive biopsy[49,54]. In addition, a unique application of FDG PET-CT is the differentiation of cerebral lesions between toxoplasmosis and lymphoma in AIDS patients, which cannot be reliably achieved with either CT or MRI[55]. In patients receiving highly active antiretroviral therapy (HAART), FDG PET-CT has been reported useful both for monitoring the response to therapy and for evaluating common side effects of treatment such as lipodystrophy, a syndrome characterized by central adiposity, peripheral fat wasting and associated metabolic abnormalities such as hyperlipidemia, hyperglycemia and insulin resistance[49,51,56]. The modality has been even suggested for assessing the lipodystrophy-inducing effect of newly developed antiretroviral regimens[49].

Newer imaging techniques have been studied for evaluation of HIV-associated multicentric Castleman disease (MCD), a rare lymphoproliferative disorder presenting with fevers, anemia and multifocal lymphadenopathy[57–58]. Preliminary findings suggest that FDG PET-CT may assist, in the management of HIV-associated MCD, in selecting appropriate sites for biopsy as well as in staging and monitoring disease activity[59–62].

FDG PET-CT in patients with fever of unknown origin

Accurate diagnosis of the cause of fever of unknown origin (FUO) can guide therapeutic intervention, reduce hospitalization time, and decrease morbidity and mortality. Localization of the source of infection can also guide biopsy procedures and therapy planning. Despite significant advances in modern diagnostic techniques, however, the underlying cause of FUO remains undiagnosed in 10% to 50% of patients[6,63–64]. Studies performed in patients with FUO indicate the FDG PET-CT appears to offer a great advantage as malignancy, inflammation and infection can be detected at the same time[65]. When systemic diseases are excluded, the modality has a high negative predictive value (up to 100%) for focal etiologies of FUO[66]. In patients with metastatic infectious foci, FDG PET-CT detected infectious complications in 75% of patients, with reported positive and negative predictive values of 91% and 99%, respectively[65]. Of note is that even though a median number of 4 diagnostic procedures had been performed prior to PET in such patients, PET identified clinically relevant new foci in 45% of cases[15,65]. The addition of FDG PET-CT in the diagnostic work-up of high-risk patients with gram-positive bacteremia was also associated with an overall decrease in mortality after 6 months from 32% to 19% because of a decrease in relapse rate[67]. Because of its high sensitivity, FDG PET-CT is commonly recommended in patients with high-risk Gram-positive bacteremia or suspected disseminated infection, especially when the responsible focus of infection remains undetected (***Fig. 6***). The technique also proved useful in identifying the source of FUO in patients with such conditions as vasculitis (***Fig. 4***), inflammatory bowel disease, sarcoidosis, painless subacute thyroiditis, cholangiolitis, etc[6,68–69].

Additionally, FDG PET-CT represents a valuable tool for early and correct diagnosis of occult sources of infection in immunocompromised patients presenting with a variety of opportunistic infections such as mycobacterium, fungal infections, herpes simplex virus, toxoplasmosis, etc[70]. Its utility in HIV-positive patients presenting with FUO has already been described in a separate paragraph. Studies performed in children with FUO showed that FDG PET and PET-CT are also valuable diagnostic tools in the pediatric population, being non-traumatic, attractive for use in children and depicting inflammation in the whole body[71].

Nevertheless, the current algorithms for FDG PET-CT indications in the diagnostic process of FUO are

not strictly evidence based and need further defining within a multidisciplinary setting, avoiding both selection and interstudy bias whenever possible[68].

FDG PET-CT in cardiovascular disease

The practical applications of FDG PET are expanding and there is increasing evidence regarding its value for assessing patients with cardiac pathology. The heart metabolizes a variety of substrates, but under normal conditions free fatty acids and glucose are the major sources of energy. In myocardial ischemia, however, oxidative metabolism of free fatty acids is decreased and exogenous glucose becomes the preferred substrate with the production of energy depending mainly on anaerobic glycolysis[72]. Cardiac imaging using FDG PET allows the evaluation of these metabolic changes and can provide important information about the functional state of myocardium, including regions of hibernating but viable tissue. In clinical practice, the assessment of myocardial viability in patients with ischemic cardiomyopathy has become an important aspect of the diagnostic work-up for revascularization surgery or heart transplantation.

Among the many viability tests, noninvasive assessment of cardiac glucose use (as a marker of viable tissue) with FDG PET is considered the most accurate technique to detect viable myocardial tissue from the myocardium with no potential for functional recovery[73]. FDG data have been shown to accurately identify patients with viable myocardium that are likely to benefit from revascularization procedures, adequately predict regional and global ventricular function improvement as well as alleviation of heart failure symptoms after revascularization, and can also be a powerful predictor of prognosis[72–73]. Many authors actually point out that PET imaging has become a standard for myocardial viability assessment[74].

Apart from a noninvasive assessment of cardiac glucose use, gated FDG PET can be used for simultaneous assessment of overall left ventricular function and calculation of such parameters as end-diastolic volume (EDV), end-systolic volume (ESV) and left ventricular ejection fraction (LVEF). Comparative studies showed an excellent agreement between gated FDG PET and cardiac magnetic resonance imaging (cMRI) in this regard. While cMRI with late gadolinium enhancement was much more sensitive in detecting moderate fibrosis, FDG PET could detect a more impaired but viable myocardium[75]. The two modalities also showed an excellent correlation for such parameters as EDV ($r=0.948$, $P<0.001$), ESV ($r=0.939$, $P<0.001$), and LVEF ($r=0.685$, $P<0.001$)[75]. EDV and ESV were underestimated, whereas LVEF was slightly overestimated by gated PET in comparison to cMRI, which should be kept in mind when comparing the two modalities. LVEF, EDV and ESV measured by gated FDG PET were also highly correlated with those obtained by single photon emission computed tomography (SPECT) modalities such as gated Tc99m sestamibi SPECT[76]. The results confirm that apart from providing accurate evaluations of myocardial viability, gated FDG PET holds the potential for simultaneous assessment of left ventricular function.

Studies evaluating right ventricular (RV) parameters also reported that gated FDG PET had moderate-to-high correlation with cMRI and cardiac computed tomography in the assessments of RV volume and ejection fraction, and that the modality proved suitable for simultaneous assessment of RV function and myocardial glucose metabolism[77]. Moreover, the increased FDG accumulation in the RV myocardium was reported to correlate with prognostic markers in patients with pulmonary hypertension including reduced exercise capacity, elevated plasma brain natriuretic peptide, and echo variables of tricuspid annular function[78].

In the chronic phase of severe myocardial infarction, the technique was reported useful for selecting suitable candidates for cell therapy. A recent pilot multimodal imaging study performed in such patients showed that perfusion enhancement obtained with bone marrow mononuclear cells in areas of chronic myocardial infarction might require an intermediate level of viability documented with FDG-PET and MRI and that totally necrotic myocardial infarction seems refractory to cell therapy[79].

In cardiac sarcoidosis, fasting FDG PET can detect the sarcoid in early stages, when fewer perfusion abnormalities and high inflammatory activity are noted, before the development of advanced fibrosis and myocardial impairment[9,80]. Comparative studies with Gallium-67 and Tc99m sestamibi scans showed that FDG PET can detect cardiac sarcoidosis when Gallium-67 or Tc99m sestamibi scintigraphy appears negative[81–82]. Studies comparing FDG PET with cMRI showed that FDG PET correlated with elevated serum angiotensin converting enzyme (ACE) levels, which was in contrast to cMRI, suggesting that FDG PET may be more useful for active disease assessment and for following treatment response[9,83]. The different distributions of the findings by the two modalities also suggest the potential of FDG PET and cMRI in detecting different pathological processes in the heart[83]. Due to frequently associated arrhythmias, a high percentage of patients with cardiac sarcoidosis have implanted

cardiac devices such as pacemakers and/or defibrillators that may interfere with an MRI examination. Cardiac sarcoid can also occur with pulmonary and mediastinal sarcoidosis. An FDG PET scan may be even more helpful in such patients for evaluating the full extent of the disease, allowing detection of clinically silent or unsuspected lesions as well as identification of potential biopsy sites[9]. Additionally, FDG PET proved particularly useful for evaluating interval changes following therapy, being commonly used to follow treatment efficacy in patients with cardiac sarcoidosis.

Abnormal patterns of cardiac FDG activity can be noted in a variety of other conditions such as lipomatous hypertrophy of the interatrial septum, epicardial and pericardial fat, increased atrial activity associated with atrial fibrillation or a prominent crista terminalis, endocarditis, myocarditis, pericarditis, etc[84]. Prominent FDG uptake involving all cardiac chambers may be also related to heart strain caused by acute pulmonary embolism[85]. The modality is also accurate for detecting acute symptomatic, proximal deep vein thrombosis. Furthermore, it has been shown that metabolic activity in thrombosed veins decreases with time, suggesting that FDG PET-CT may be helpful in assessing the age of the clot[86]. FDG uptake in vascular walls can be noted in vasculitis caused by a variety of autoimmune, infectious or inflammatory conditions as well as in arteriosclerosis. In vessels affected by atherosclerosis, FDG accumulates in plaque macrophages and its uptake is correlated with macrophage density[87]. Since vulnerable and stable plaques can be distinguished by quantitative analysis of FDG uptake, FDG PET has the potential to be used for predicting thrombosis events and risk-stratification in patients with atherosclerotic disease[87–88]. Delayed time-point FDG PET studies performed in patients with atherosclerosis further suggest utilization of 3-hour delayed imaging to obtain optimal data for the detection and quantification of atherosclerotic plaque inflammation in human arteries as delayed imaging enhances assessment of atherosclerotic plaque inflammation[89]. The visual grading of vascular FDG uptake and its pattern of distribution may help discriminate arteritis from atherosclerosis[90].

Last but not least, it should be also remembered that cardiac FDG uptake in fasted patients has been widely reported as variable. Focal or regional increased FDG activity can be observed in healthy subjects within papillary muscles, the atria, posterolateral wall of the left ventricle and distal anteroapical region, as well as left ventricular base[84]. Understanding the range of these normal patterns of cardiac FDG activity is crucial for differentiating them from cardiac pathology.

FDG PET-CT in other conditions

FDG PET-CT is increasingly used in a variety of other non-oncologic conditions interconnecting to different medical disciplines.

In neurology, FDG PET is playing an important role in the evaluation of various epileptic syndromes, where it can be used alone or in combination with brain single-photon emission computed tomography (SPECT). Overall, ictal SPECT has the highest diagnostic sensitivity for both temporal and extratemporal lobe epilepsy, and PET is known to have high sensitivity for the evaluation of extratemporal lobe epilepsy.[91] When both studies are used together, however, they can provide complementary information. For example, interictal FDG PET and ictal subtraction SPECT of the brain have been shown to be valuable tests in the presurgical evaluation of epilepsy[92]. FDG PET also shows hypometabolism in a majority of patients with nonlesional temporal lobe epilepsy, even in the absence of hippocampal atrophy[91,93]. A separate entity of ''MRI-negative PET-positive'' temporal lobe epilepsy has even been described[93]. Studies performed in the pediatric population showed that PET used for brain mapping in children provides the surgeon with strategic preoperative information not readily attainable with traditional invasive Wada testing or intraoperative cortical stimulation; it may also improve the outcome of extratemporal resections by allowing aggressive seizure focus resection[94]. Additionally, serial brain maps may optimize timing for surgical intervention by demonstrating reorganization of eloquent cortex often seen in younger children after cortical injury[94]. The modality also provided new insights and proved helpful in the clinical evaluation of patients with a variety of other disorders including cognitive impairment and dementias, neurodegenerative diseases, schizophrenia, Huntington's disease, Creutzfeldt-Jakob disease, encephalitis caused by different etiologies, etc[95–99]. For instance, in patients presenting with cognitive impairment, FDG PET is particularly useful for differentiating Alzheimer disease from other degenerative dementias such as frontotemporal dementia (FTD) and dementia with Lewy bodies (DLB). FDG PET has also been used in the study of mild cognitive impairment to accurately predict the subsequent decline to Alzheimer disease[97]. Given the increasing variety of applications of PET imaging of the brain and their expanding interconnections to such disciplines as neurology, psychiatry, neuropsychology and cognitive neuroscience, the area represents a separate topic and is therefore only briefly mentioned in this paper.

FDG PET-CT applications in endocrine and neuroendocrine pathology are similarly expanding. As

both type 1 and type 2 diabetes mellitus are associated with a functional loss of β-cell mass, most efforts to cure diabetic patients have focused on preserving β-cell mass and its function[100]. With recent advances in islet cell transplantation techniques, FDG PET has the potential to image transplanted islets and evaluate their location, distribution, and function following transplantation. Currently, two modalities are being assessed for this purpose: FDG PET and MRI. Both techniques require that *ex vivo* islets be labeled, before transplantation, with 2-[fluorine 18]fluoro-2-deoxy-D-glucose (FDG) for PET and superparamagnetic iron oxide (SPIO) for MR imaging. Experimental studies have shown that the labeled islets may be visualized at both PET and MR imaging, thus allowing monitoring of the success of engraftment[101–103]. The main advantages of FDG PET-CT is that it is readily available in most centers performing islet transplantation and that it allows real-time measurement of islet survival and distribution after transplantation[102], while the main limitation is related to a relatively short half-life of FDG, which limits the visualization of the transplanted islet to the first few hours following transplantation[101].

Metabolic imaging with FDG may also provide useful information in patients with other endocrine disorders and systemic diseases such as thymic pathology, focal and diffuse thyroid diseases, primary hyperparathyroidism, ectopic Cushing syndrome, amyloidosis, etc[104–111]. For example, studies performed in patients with primary hyperparathyroidism showed that FDG PET is more sensitive than Tc99m sestamibi SPECT in the preoperative localization of parathyroid adenomas[108]. In patients with Graves' disease, FDG PET may provide information on the biological activity of Graves' disease as well as on early radiation effects[109], while in myasthenia gravis, selective use of FDG PET was reported useful in differentiating thymoma from hyperplasia, especially when CT scan is controversial[104]. Published reports indicate that FDG PET-CT may also have the potential for monitoring the development of amyloid lesions[110–111]. However, despite the expanding areas of FDG PET applications in non-oncologic disorders, new prospective studies are needed to determine the place of FDG PET in the diagnostic work-up of many of these conditions.

Conclusion

The clinical applications of FDG PET-CT are rapidly expanding, involving many clinical disciplines and areas of research. The modality has become a valuable tool in the diagnosis, treatment evaluation and follow-up of patients with a variety of infections and inflammatory conditions and is already the gold standard for some indications. The modality proved especially useful in detecting the source of fever of unknown origin, including in immunocompromised and HIV-positive subjects, by showing an overall sensitivity and specificity of over 90% for localization of focal pathology in subjects presenting with unexplained fever, weight loss, or confusion. It may also provide valuable information related to the anatomic correlates of HIV progression without the need for biopsy and for monitoring the response to therapy. In cardiology, FDG PET-CT imaging has become a standard for myocardial viability assessment and also holds the potential for simultaneous assessment of left ventricular function. In patients with cardiac sarcoidosis, FDG PET-CT and cMRI may complement each other by providing valuable information related to disease extent and treatment response. An FDG PET-CT scan may be especially helpful in patients with simultaneous extracardiac lesions, allowing evaluation of the full extent of the disease and identification of potential biopsy sites. Promising results have also been obtained for a variety of other potential applications, including risk-stratification for atherosclerotic disease. In neurology, FDG PET-CT is playing an important role in the evaluation of various epileptic syndromes as well as in the clinical assessment of patients with a multitude of other disorders, including cognitive impairment and dementias. With recent advances in the islet cell transplantation techniques, FDG PET-CT has the potential to image transplanted islets and evaluate their location, distribution, and function following transplantation. The modality may also provide useful information in patients with a variety of other endocrine and systemic disorders, having the advantage of being able to screen the whole body. However, despite the expanding areas of metabolic imaging with FDG, new prospective studies are needed to determine the place of FDG PET-CT in the diagnostic work-up of many of these conditions.

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