

# FDG PET/CT in the detection of infections and inflammations

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## SUMMARY

Detection of inflammation/infection still remains great clinical problem. That is why nuclear medicine procedures still play a significant role regarding this issue. There has been attempts for detection of infection/inflammation using  $^{67}\text{Ga}$ -citrate,  $^{99\text{m}}\text{Tc}/^{111}\text{In}$  labeled white blood cells,  $^{99\text{m}}\text{Tc}/^{111}\text{In}$  labeled human immunoglobulin,  $^{99\text{m}}\text{Tc}$  labeled antigranulocyte antibodies (whole or fragments),  $^{99\text{m}}\text{Tc}$  labeled antibiotic,  $^{99\text{m}}\text{Tc}$  nanocolloid as well as different other radiopharmaceuticals. However, there has not been discovered the ideal one. Recently,  $^{18}\text{F}$ -FDG PET begins to play a significant role.

**Key words:** Positron-Emission Tomography and Computed Tomography; Diagnostic Imaging; Infection; Inflammation; Granulomatous Disease, Chronic; Fluorodeoxyglucose F18

Radiopharmaceutical  $^{18}\text{F}$ -fluorodeoxyglucose (FDG) is transported into cells using glucose transporters. It is phosphorylated by hexokinase to  $^{18}\text{F}$ -2'-FDG-6 phosphate and it is not further metabolized. The degree of cellular FDG uptake is a reflexion of cellular metabolic rate as well as of number and expression of glucose transporters (1–3). Increased FDG uptake in malignant tumors is mainly and usually due to an increased number and expression of glucose transporters, as well as because of increased glucose metabolism. In inflammation, FDG uptake in activated neutrophils, lymphocytes, and macrophages occur due to increased numbers of cell surface glucose transporter proteins, increased intracellular hexokinase and phosphofructokinase levels, particularly after cellular stimulation by multiple cytokines (3–6). After FDG phosphorylation, structural changes made by a hexose–phosphate bond prevent it from being catabolized or transported back into the extracellular space. This event is called “metabolic trapping” and is the the main source of energy in chemotaxis and phagocytosis. The hexose-monophosphate shunt is stimulated by phagocytosis, which is the cause of high FDG uptake. Neutrophils take up FDG during acute phase of inflammation while macrophages and polymorphonuclear leukocytes take up FDG during chronic phase. In sterile inflammation, FDG is mainly taken up by neutrophils and macrophages. Inflammatory cells increase the expression of glucose transporters when they are activated, and multiple cytokines and growth factors can facilitate glucose transport even without increasing the number of glucose transporters. Glucose-6-phosphatase is decreased in tumor cell, while it remains the same in inflammatory cells causing washout of FDG. That is why, on delayed scans, FDG accumulation is supposed to be decreased.

The main indications for detection of infection with FDG positron emission tomography with computed tomography (PET/CT) are bone infections osteomyelitis, spondylodiscitis, diabetic foot, prosthesis, fever of unknown origin (FUO), graft infections, immunocompromised host infections and other abdominal and chest infections. The main indications for detection of inflammation/granulomatous diseases are vasculitis, polymyalgia reumatica, sarcoidosis/tuberculosis, rheumatoid arthritis as well as inflammatory bowel disease/Crohn’s disease. Sometimes these two categories overlap.

## OSTEOMYELITIS

Detection of osteomyelitis still remains a great clinical problem. FDG PET/CT is not indicated in detection of acute osteomyelitis because it can be easily discovered with other methods. According to the results in literature, sensitivity (100%), specificity (87.5%) and accuracy (90.9%) of FDG PET/CT for this indication are very high (7) (Figures 1, 2). Although in normal healing bone uptake can be high because the same cells are present as in infection, it is reported that FDG appears to normalize rapidly, up to 4 month after surgery following traumatic or surgical fractures as fibroblast predominate in normally healing bone (8). FDG-PET has the highest diagnostic accuracy for confirming or excluding the diagnosis of chronic osteomyelitis. Leukocyte scintigraphy has an appropriate diagnostic accuracy in the peripheral skeleton, but FDG-PET is superior for detecting chronic osteomyelitis in the axial skeleton (9). Furthermore, negative PET finding excludes presence of the disorder. However, future studies are needed to define the role of FDG in the evaluation of musculoskeletal infection.

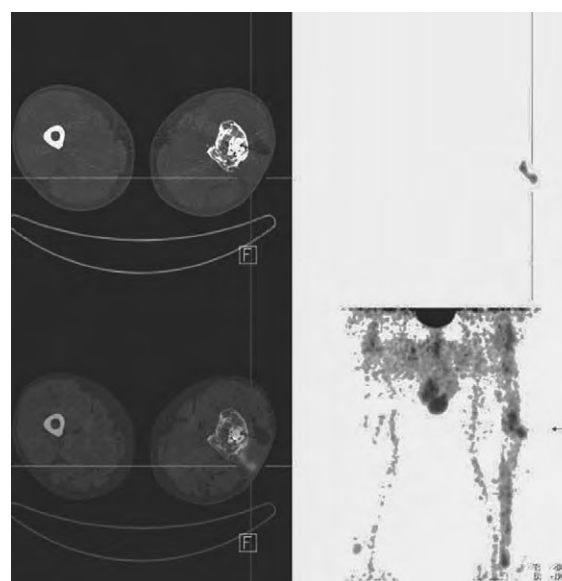


Figure 1. High FDG uptake in the left femur: osteomyelitis

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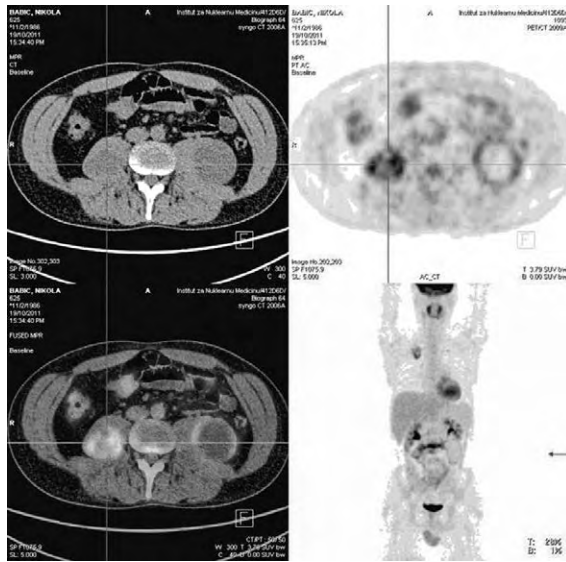
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**Figure 2. High FDG uptake in L3 and L4 with bone destruction and destruction of intervertebral disc with abscesses in both psoas muscles-infection**

Concerning spondylodiscitis, PET/CT is better than scintigraphic techniques for detection of disease, differentiation of infection from degenerative changes and exclusion of disc space infection if MR is equivocal. Reported sensitivity of FDG PET/CT in this indication is 95%, specificity 100% and accuracy 97% (10, 11). Unsuspected osteomyelitis is frequent in persistent diabetic foot ulcer and better diagnosed by MRI than by <sup>18</sup>F-FDG PET or <sup>99m</sup>Tc-antigranulocyte antibodies. Only if MRI is inconclusive, conventional radionuclide imaging or FDG-PET/CT might help in the diagnosis of osteomyelitis (12). In the detection of metallic implants infection after trauma, it is superior to MR and CT because it is not affected by artifacts, especially in chronic infections (sensitivity is around 100% and specificity approximately 90%) (13).

Peri-prosthetic uptake is similar in infection and aseptic loosening, so it is not easy to differentiate between infection and inflammatory reaction to prosthesis meaning that infection vs. loosening differentiation has limited accuracy (50-70%). There has not still been made final conclusion in different studies in differentiation septic from aseptic loosening in total hip replacement. Moreover, it has lower specificity than bone scintigraphy combined with leukocyte scintigraphy. PET/CT findings are more accurate in hip than knee prostheses. It is difficult to differentiate between metal-wear induced chronic inflammatory and infectious processes seen around prostheses. However, typical FDG uptake patterns in different pathologic conditions still need to be defined (14).

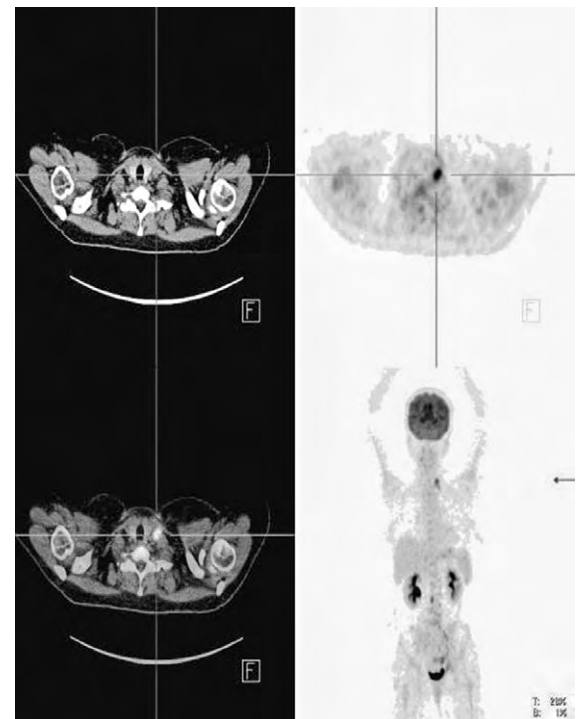
### ACQUIRED IMMUNODEFICIENCY SYNDROME

It has been reported (15) that FDG PET was 92% sensitive and 94% specific for localizing abnormalities that required treatment. However, it was not possible to distinguish infection from tumor at FDG PET but it is possible to differentiate lymphoma from toxoplasmosis.

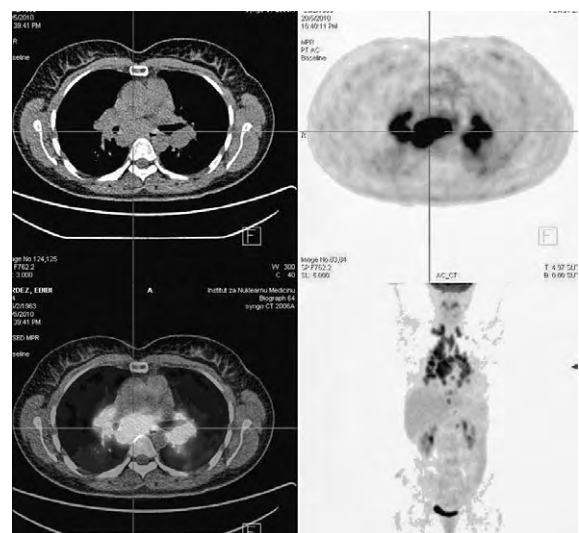
### FEVER OF UNKNOWN ORIGIN (FUO)

Detection of FUO is still a great clinical problem. It considers conditions where temperature is higher than 38.3°C, which occur repeatedly, with duration of at least 3 weeks, with uncertain source after one week of investigation with conventional techniques and without diagnosis after

appropriate inpatient or outpatient evaluation. FUO can be caused by tumor, infection, inflammatory condition, or other conditions. Even 25% of patients with FUO remain without diagnosis. FDG PET/CT is helpful in 16-55% according to different authors (16). This range is large because definition of FUO differs, patient recruitment is different (classic FUO or postoperative sepsis), there is no standardized FDG-PET diagnostic protocol and there is no final diagnosis in all patients. FDG PET/CT showed specificity 86% and sensitivity 84% as well as exact localization of lesions (17) (Figures 3, 4). Negative FDG PET findings make it very unlikely that a morphologic origin of the fever will be identified.



**Figure 3. FDG uptake in left neck, left paraaortal and right and left parailiac Igl, and soft tissue presacral zone: FUO**



**Figure 4. Visible zones of intensive FDG accumulation in infiltrative lesions in both lungs and mediastinal lymph nodes: sarcoidosis.**

As a difference from FUO, where sensitivity may be more important than specificity in the evaluation of patients, specificity is more important in the evaluation of focal infection, most often after surgery. In patients with suspected focal infection in whom nuclear medicine methods are suggested, a discrete abnormality has frequently been detected but not precisely characterized with anatomic imaging. Often, these patients are suspected of having a postoperative infection or have a history of tumor, and the PET/CT is demanded to help differentiate infection from postoperative changes or tumor (18). However, there are numerous limitations of FDG in differentiating infection from tumor. Although the role of FDG in the evaluation of postoperative infection has not been extensively studied, persistent FDG uptake in uninfected surgical incisions has been observed. It is suggested that at least several weeks have to elapse between surgery and FDG PET to minimize the possibility of false-positive results secondary to tumor or postoperative changes (19).

### PET/CT IN ENDOVASCULAR GRAFT INFECTION

Co-registration with CT helps to determine exact location of the focus and differentiate if it is in the graft or surrounding tissue. Chronic aseptic inflammation in synthetic graft material can cause FDG uptake. FDG PET/CT sensitivity for this indication is 93% and specificity 91%, (20, 21). It can also be used for detection of infection in cardiac valve prosthesis.

### PET/CT IN INFLAMMATION

Sarcoidosis is a chronic inflammatory condition of unknown cause. Assessment of disease activity mainly determines the type of therapy. Thus, although FDG PET is not useful for initial diagnosis, it will probably be useful for evaluating the extent of active disease and monitoring response to therapy in patients with known sarcoidosis (22). Vasculitis is inflammation and necrosis of blood vessel walls. The diagnosis of vasculitis is complicated by a lack of specific signs and symptoms. Imaging is often used to confirm a suspected diagnosis in the absence of histologic proof, as well as to identify sites for biopsy (23). FDG uptake in giant cell arteritis, Takayasu arteritis, aortitis, and unspecified large vessel vasculitis has been described.

The role of FDG PET/CT has also been under evaluation in rheumatoid arthritis, polymyalgia rheumatica, inflammatory bowel /Crohn's disease, brain inflammation, cardiovascular inflammatory and infective process and other indications.

### CONCLUSION

FDG PET is a promising modality in the diagnosis of infection and inflammation. FDG PET may be of limited usefulness in diabetic foot, infected prosthesis (bone, vascular), rheumatoid arthritis, inflammatory bowel / Crohn's disease, endocarditis and other indications. However it gains increasing importance in assessing FUO, spinal osteomyelitis, vasculitis, and sarcoidosis, perhaps even becoming the radionuclide procedure of choice in the evaluation of some or all of these entities.

### Conflict of interest

We declare no conflicts of interest.

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