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Evolving Role of Positron Emission Tomography in the Management of Patients With Inflammatory and Other Benign Disorders

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Fluoro-2-deoxyglucose (FDG) positron emission tomography (PET) has evolved from a research imaging modality assessing brain function in physiologic and pathologic states to a pure clinical necessity. It has been successfully used for diagnosing, staging, and monitoring a variety of malignancies. FDG-PET imaging also is evolving into a powerful imaging modality that can be effectively used for the diagnosis and monitoring of a certain nononcological diseases. PET has been shown to be very useful in the diagnosis of osteomyelitis, painful prostheses, sarcoidosis, fever of unknown etiology, and acquired immunodeficiency syndrome. Based on recent observations, several other disorders, such as environment-induced lung diseases, atherosclerosis, vasculitis, back pain, transplantation, and blood clot, can be successfully assessed with this technique. With the development and the introduction of several new PET radiotracers, it is expected that PET will secure a major role in the management of patients with inflammatory and other benign disorders.

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Positron emission tomography (PET) has proven to be a powerful imaging modality in the management of patients with a variety of malignancies. However, because of its extraordinary power as a molecular imaging technique, in recent years, the domain of applications regarding this technique has expanded enormously in assessing other disorders, in particular inflammatory processes. The role of PET also as an imaging technique in drug discovery and development is rapidly evolving, and its contributions to both disciplines (assessing benign disorders and developing new drugs) will rival those that already have been achieved in malignant diseases.

Basis of Using PET in Infection and Inflammation

Compared with current radiological imaging modalities such as computed tomography (CT), magnetic resonance imaging (MRI), and ultrasound, PET as a molecular imaging technique is capable of detecting the disease in early stages and long before visible structural changes are noted with conventional methods. PET is a very safe, noninvasive methodology that can image the entire body in a reasonably short period of time. It is not affected by metallic implants and can be performed in very sick patients, including those with immunocompromised states. To date, most studies reported in the literature for the diagnosis of infection and inflammation have been performed using 18-Fluoro-2-deoxyglucose (FDG), which is the most frequently used PET radiotracer in the world because of its availability, favorable half-life, and high concentration in either benign or malignant lesions.

Malignant cells are known to have enhanced glycolysis,[1] partly because of increased levels of glucose transporter proteins, and to a great extent, because of the levels of the enhanced hexokinase activity in the cells.[2,3] Similarly, benign processes such as infection, inflammation, and granulomatous diseases appear to have increased glycolysis[4] and are readily visualized by FDG-PET imaging. By now, it is well established that inflammatory cells have enhanced glycolysis when they are stimulated,[5] and this has been mainly attributed to the high number of glucose transporters in these cells and partly to the enhanced affinity of these transporters for this substrate.[6-8] Multiple in vitro studies have been performed to assess the feasibility of labeling FDG to the leukocytes, which have demonstrated favorable results.[9,10] An animal and test tube study reported by Ishimori et al[11] demonstrated that activated lymphocytes in the concanavalin A-mediated acute inflammatory tissues revealed increased FDG uptake in both the in vitro and in vivo models. Heelan et al[12] noted that FDG uptake was 1.5 to 2 times higher in allogeneic than in syngeneic grafts when using a mouse skin transplantation model, which correlated with the levels of T-cell infiltrate seen on

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Table 1 Variety of Infections and Inflammatory Diseases Detected by PET

Several Reported Infections and Inflammatory Processes	
Tahara et al,[19] Okazukmi et al[20]	Abdominal and pelvic abscesses
Okazumi et al[20]	Liver abscess
Sasaki et al,[21] Tsuyuguchi et al[22]	Brain abscess
Yen et al[23]	Lung abscess
Kaya et al[24]	Renal abscess
Bleeker-Rovers et al[25]	Hepatic and renal cyst infection
Zimny et al,[26] Schroder et al[27]	Salpingoophoritis and tubo-ovarian abscess
Kapucu et al[28] Bakheet et al,[29] Tahon et al,[30] Jones et al[31,32]	Pneumonia
Zhuang et al,[33] Sugawara et al,[34] Kalicke et al,[35] Guhlmann et al[16,36]	Osteomyelitis
Zhuang et al,[37] Vanquickenborne et al,[38] Cremerius et al[39]	Infected arthroplasty
Bakheet et al,[40] Hara et al[41]	Tuberculosis
Reuter et al[42]	Echinococcosis
Ozsahin et al,[43] Franzius et al[44]	Aspergillosis
Zhuang et al,[45] O'Doherty et al[46]	Atypical mycobacterial infection
Bakheet et al[47]	Mastitis
Kresnik et al,[48] Hannah et al,[49] Meyer et al[50]	Enterocolitis
Tomas et al[51]	Infectious mononucleosis
Yasuda et al[52]	Sinusitis
Brudin et al,[15] Lewis et al,[53] Cook et al,[54] Yamada et al,[55] Yamagishi et al,[56] Yasuda et al[57]	Sarcoidosis
Taylor et al,[58] Alavi et al[59]	Asthma
Gysen et al[60]	Myositis
Yasuda et al[61]	Thyroiditis
Imran et al[62]	Mediastinitis
Nunez et al[63]	Gastritis

the histologic examination. Using microautoradiography, Kubota et al[13] showed that FDG uptake was higher in tumor-associated macrophages and young granulation tissues than in tumor cells. In an experimental rat model of bacterial infection with *Escherichia coli,* autoradiographs showed that FDG rapidly accumulates at the sites of bacterial infection and in reactive lymph nodes with a high target-to-background ratio compared with the other tracers, such as radiolabeled thymidine and L-methionine, gallium-67 citrate (67Ga-citrate), and iodine-125 human serum albumin (^{125}I-HSA).[14]

The role of FDG-PET imaging has been extensively examined in several aseptic inflammatory processes, as well as in a wide variety of infections, and there is growing consensus about its importance in evaluating such disorders.[15-18] FDG-PET can successfully detect numerous common infections and inflammatory conditions as enumerated in Table 1.

In addition to FDG, many radiopharmaceuticals are used for scintigraphic detection of infectious diseases and inflammatory processes, including 67Ga-citrate; 111-Indium, and 99mTc-HMPAO (hexamethylpropylene-amine-oxime) labeled leukocytes; 99mTc-labeled-antigranulocyte monoclonal antibodies; 111-Indium, and 99mTc-labeled human immunoglobulin. Several other radiopharmaceuticals are under investigation for imaging infectious diseases and inflammation and include radiolabeled antibodies,[64,65] radiolabeled receptor-binding proteins/peptides,[66,67] radiolabeled liposomes,[68,69] and radiolabeled antibiotics.[70]

FDG-PET has several advantages over other nuclear medicine techniques for the diagnosis of infectious diseases, which include securing results within a short period of time (1.5-2 h), generating images with high spatial resolution and target to background contrast (contrast resolution), providing accurate results in axial bony structures, and delivering a relatively low radiation dose.[71] These advantages combined have allowed high interobserver agreement about the presence or the lack of disease activity and outstanding sensitivity for detecting chronic low-grade infections.

Dual time point FDG-PET imaging has been proposed as a method to differentiate between malignant and inflammatory processes in the settings where such distinction is essential for optimal management of the patient. It has been shown that the standard uptake values (SUVs) of the inflammatory or benign lesions remain stable or decrease over time, whereas those of the malignant tissues increase on later images.[72] Using dual time point scanning with a threshold value of 10% increase between scan 1 and scan 2, Matthies et al[73] noted that FDG-PET reached a sensitivity of 100% and a specificity of 89% in differentiating benign pulmonary nodules from malignant lung tumors. By correcting the SUV for the body surface area and by increasing the time interval between injection of FDG and imaging, Conrad and Sinha[74] showed improvement in the ability of FDG-PET in discriminating between benign and malignant conditions of the central thoracic lesions.

Specific Clinical Applications

Acute and Chronic Osteomyelitis

PET has a limited role in the diagnosis of uncomplicated cases of acute osteomyelitis, which is readily diagnosed by combining history and physical examination, biochemical markers such as white blood cell count, erythrocyte sedimentation rate, C-reactive protein, plain roentgenograms, bone scan, and MRI.[75] Currently, the presence of chronic osteomyelitis also is suspected based on clinical, laboratory, and imaging studies. However, the biochemical markers lack sensitivity and specificity,[76,77] and the gold standard is to obtain a biopsy for pathological confirmation of the suspected infected bone.[78] None of the current conventional imaging techniques is

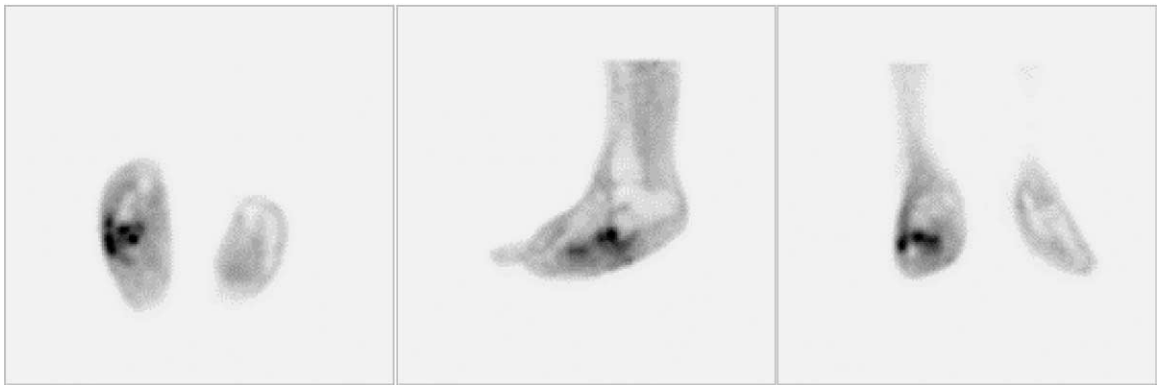

Figure 1 Osteomyelitis in a diabetic patient which involves most of the tarsal bones and the base of the fourth and fifth metatarsals. FDG-PET clearly demonstrated the extent of the disease.

satisfactory in confirming or excluding the presence of osteomyelitis. CT and MRI can provide excellent anatomic details; however, they both have limited value in optimal assessment of postsurgical changes from infection and have a limited role for this purpose in the presence of metallic implants.[79-81] The use of three-phase bone scan in combination with labeled leukocyte scan has revealed a good accuracy in the diagnosis of chronic osteomyelitis in the extremities.[82] However, this method has a low accuracy in the axial skeleton and at other sites with high concentration of the red marrow, in low-grade chronic infections, in the presence of soft tissue infection, and after trauma or surgery.[81,83-86] The combination of leukocyte imaging with bone marrow scanning or with gallium scan has improved the sensitivity and specificity of this technique. However, performing multiple scans, in addition to the substantial costs and the unavoidable high radiation doses, is time consuming and is taxing for the patient and the technical staff. Therefore, the search for imaging methods that could overcome these difficulties has continued.

Several studies have made an attempt to determine the role of FDG-PET in diagnosing patients with chronic osteomyelitis (Fig. 1). Guhlmann et al[16,36] reported a higher accuracy for FDG-PET than antigranulocyte antibody scintigraphy in imaging the central skeleton for infection in patients with suspected chronic osteomyelitis. In a prospective study that included patients with recent surgery, De Winter et al[87] reported a sensitivity of 100%, a specificity of 86%, and an accuracy of 93% in 60 patients with suspected chronic musculoskeletal infections. Another prospective study by Meller et al[88] on 30 patients with suspected active chronic osteomyelitis concluded that FDG-PET is superior to 111-indium-labeled leukocyte imaging in the diagnosis of chronic osteomyelitis in the central skeleton. PET holds a great promise in the diagnosis of chronic osteomyelitis, and a negative PET study essentially rules out osteomyelitis.[33] The case of chronic osteomyelitis detected by FDG-PET but not MRI nor antigranulocyte antibody scintigraphy has been reported.[89] It is known that increased FDG uptake at the fracture sites only lasts relatively a short period of time.[90,91] Therefore, past history of fracture or surgical trauma is unlikely to cause false-positive result in the evaluation for chronic osteomyelitis. In contrast to other nuclear medicine modalities, such as gallium scintigraphy and labeled leukocyte imaging, FDG has high resolution and can distinguish soft tissue infection from osteomyelitis (Fig. 2).[92] We expect that FDG-PET imaging will be used routinely in the near future to determine the presence or the absence of an infectious focus, to monitor response to antimicrobial treatment, and to develop certain criteria for deciding when the treatment can be safely stopped.

PET in the Evaluation of Prostheses

Assessment of suspected superimposed infection in prosthetic implants has been the subject of multiple research studies during the past several years. Loss of fixation (aseptic loosening) is a major long-term complication of total hip arthroplasty and is the most common indication for revision of prosthesis. In patients with suspected or confirmed loosening of the prosthesis, the possibility of superimposed infection, which is a very serious complication, should be considered in most clinical settings. Pain is a common manifestation of both complications, and the distinction between the two is very difficult in most clinical circumstances and it may be impossible at times.

The combination of leukocyte scan and sulfur colloid bone marrow scan has a reasonable accuracy in detecting infected prosthesis.[93] However, this test is complex and expensive, requires in vitro

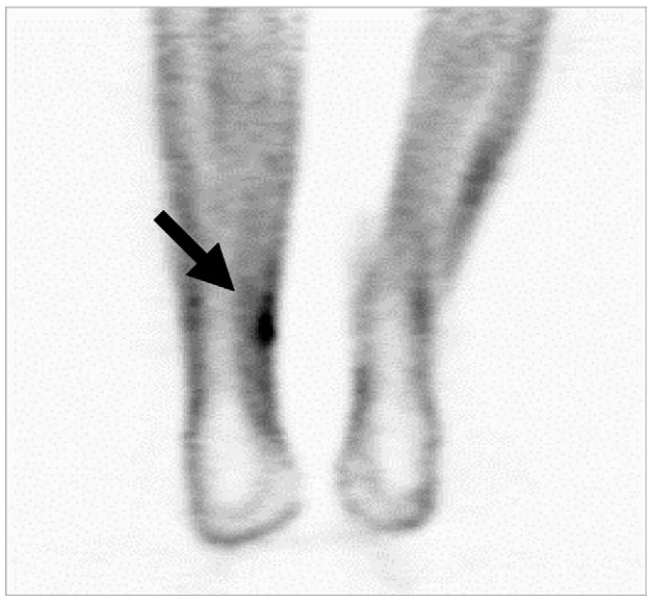

Figure 2 Cellulitis of the right lower leg in a 70-year-old male with diabetic skin ulcer is clearly visualized and delineated on FDG-PET image and, therefore, osteomyelitis in the adjacent bone is ruled out.

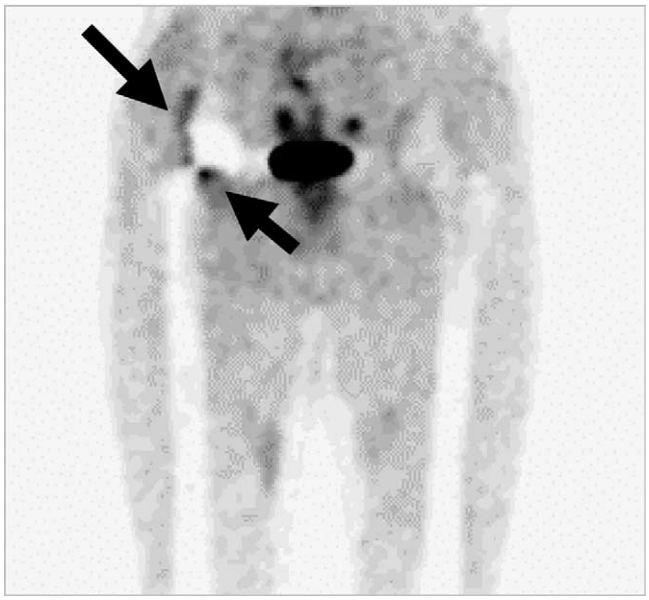

Figure 3 Coronal images of the pelvis showing normal FDG uptake around the head and neck of the right hip prosthesis which appeared without complications based on clinical assessment.

labeling of the cell with potential for contamination with pathogens or mixing blood samples among patients, and requires at least 24 h for completing the procedure. In addition, the low sensitivity and specificity reported by Scher et al[94] (77% sensitivity, 86% specificity, 54% and 95% positive and negative predictive values, and 84% accuracy) for the prediction of infection further diminishes enthusiasm for this procedure. FDG-PET has a great potential for detecting infection in hip prostheses, and to lesser extent in knee prostheses. The use of PET is advantageous over anatomic imaging modalities because it is not affected by the metal implants[35,95] and it also provides better resolution images than those of the conventional nuclear medicine techniques. In a study involving 36 knee prostheses and 38 hip prostheses, our group[37] reported that the respective sensitivity, specificity, and accuracy of FDG-PET for detecting infection was 90%, 89.3%, and 89.5% for hip prostheses and 90.9%, 72.0%, and 77.8% for the knee prostheses. It is unclear why FDG-PET is more accurate in the diagnosis of periprosthetic infection in the hips in comparison to that in the knees. The criteria for diagnosing periprosthetic infection with FDG-PET is essential for optimal utilization of this method because interpreting any sites of increased periprosthetic uptake as positive for infection will result in low specificity.[96] Increased FDG uptake around the neck and/or head of the prosthesis is very common and should not be interpreted as a finding suggestive of infection (Fig. 3).[97] Increased FDG uptake that is present along the lower portion of the interface between hip prostheses and bone commonly is associated with infection (Fig. 4).[98] Manthey et al[99] proposed that intense glucose uptake in the bone prostheses interface should be reported as being positive for infection, and visualizing an intermediate degree of uptake at these sites suggesting loosening, and uptake only in the synovia was considered as synovitis. The current criteria for assessing knee prostheses for infection result in high false positive diagnoses of infection.[100] Nonspecific increased FDG uptake around the head or neck portion of the hip prosthesis after arthroplasty can persist for an extended period of time.[97] This pattern is seen with similar appearance in patients with loosening, and therefore it does not affect the accuracy of the test in the diagnosis of infection. However, at present time, the potentials of FDG PET in the evaluation of prostheses have not been fully defined. Some authors[96] believe that FDG-PET has excellent sensitivity but poor specificity whereas other reports[101] indicate that the specificity of FDG-PET is good but the sensitivity is less than optimal in this clinical setting. These different conclusions might be the result of different interpretation criteria used by these investigators. Apparently, more investigations are needed to define the roles of FDG-PET in the evaluation of prostheses.

Fever of Unknown Origin (FUO)

FUO was initially defined as a fever of higher than 38.3°C that has been documented on several occasions, duration of the fever for at least 3 weeks, and the source being uncertain after 1 week of comprehensive investigation with conventional techniques as an inpatient in the hospital setting. This definition was later revised by eliminating the requirement for in-hospital evaluation and redefining the latter criterion to include at least in or outpatient evaluation for a minimum of 3 days or three outpatient visits. Three major categories that account for the majority of FUO are infections, malignancies, and collagen vascular or autoimmune diseases. Infection is the most frequent cause of FUO, followed by neoplasm, and then noninfectious inflammatory diseases. The diagnostic approach in FUO includes a thorough history and physical examination, laboratory tests, and conventional radiographic studies. Early identification and localization of an infectious or inflammatory process can be critical for the management of these patients. CT scanning of the abdomen has nearly replaced exploratory laparotomy in this population and is used in nearly all patients with FUO. This in turn has increased the number of positive results when subsequent invasive procedures are performed.

It has been reported that gallium-67 and 111-indium-labeled leukocytes have an overall higher yield than CT or ultrasound for detecting the sites of the disease.[102,103] Currently gallium-67 scanning is the most commonly used radiotracer for the evaluation of FUO because it can visualize malignancies, as well as inflammatory and granulomatous disorders.[104] Scintigraphic imaging has the advantage of detecting early changes at the molecular level before any structural changes have occurred (therefore it has higher sensitivity

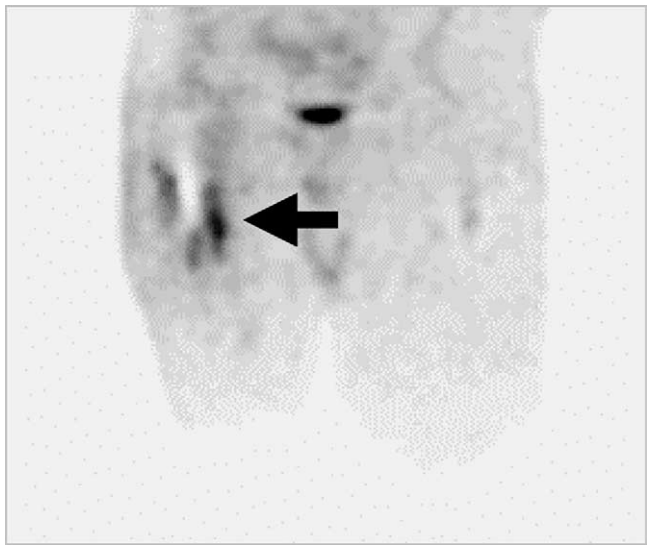

Figure 4 Increased FDG uptake around the shaft of the right hip prosthesis consistent with infection in a 48-year-old male with painful right hip. Revision surgery confirmed the presence of infection.

than anatomical imaging techniques), and it also can differentiate between necrotic and viable tissues.

PET has the potential to replace other nuclear medicine imaging techniques in the evaluation of patients with FUO. FDG-PET is advantageous over gallium-67 because it can image the whole body in a short time, has high spatial resolution and provides high-quality images, and delivers relatively low radiation dose to the patient. Sugawara et al[34] in a small series of patients showed that FDG-PET can correctly identify the presence or absence of infection in 10 of 11 patients and missed the source in 1 diabetic patient with high blood sugar level. Stumpe et al[18] reported 98% sensitivity, 75% specificity, and 91% accuracy for FDG-PET in 39 patients with suspected infections. In a prospective study that compared the role of FDG-PET imaging with that of gallium scintigraphy in patients with FUO, Blockmans et al[105] studied 58 consecutive cases of fever of unknown origin. In 38 patients (64%) a final diagnosis was established. The results were comparable between the two, but FDG imaging was considered superior because it provided quick results, and therefore the authors suggested that gallium scintigraphy could be replaced by the FDG imaging in the future. Meller et al[106] compared FDG and gallium scanning in patients referred for FUO and reported a sensitivity of 81% and a specificity of 86% for FDG-PET in detecting the cause of the fever and a sensitivity and specificity of 67% and 78%, respectively, for gallium scanning.

Because of its high sensitivity in detecting malignant lesions, infections, as well as various inflammatory processes, FDG-PET has the potential to play a central role in the management of patients with FUO. In a prospective study on 18 patients with postoperative fever, Meller et al[107] reported a sensitivity of 86% and specificity of 100% for FDG-PET in detecting infections outside the surgical wound. However, the specificity of FDG-PET in detecting infections within the surgical wound was only 56%, whereas the sensitivity was 100%. The low specificity was attributed to the accumulation of the tracer in granulation tissue at the site of surgical intervention. Bleeker-Rovers et al[108] reported that in certain cases, such as recurrent fever, and in patients referred for a second opinion, the percentage of patients with FUO in whom no diagnosis could be made with FDG-PET was of 46%.

Common causes of fever of unknown origin, which can be detected by PET, include a variety of malignancies and different inflammatory/infectious processes, such as inflammatory bowel disease,[17] pelvic inflammatory disease,[105] osteomyelitis,[36] sarcoidosis,[53] and aortitis.[109]

Acquired Immunodeficiency Syndrome (AIDS)

Scharko et al[110] employed PET imaging in a model of simian immunodeficiency virus-infected rhesus macaque to define disease stage and sites of immune system activation in response to virus infection. This demonstrated that this modality can be used effectively to evaluate the distribution and the activity of infected tissues in a living animal without biopsy for an extended period of time. In a prospective study by the same group on 15 HIV-1-infected patients, they noted an association between the pattern of lymphoid tissue activation and the clinical stage of the disease.[111] PET was useful in demonstrating that in the acute stages there is activated lymphoid tissue in the head and neck region with some splenic involvement, a generalized pattern of peripheral lymph-node activation at the mid-stages, and involvement of abdominal lymph nodes during the late disease.[110]

PET has a major role to play in the management of human immunodeficiency virus (HIV)-infected patients, especially in those with the central nervous system (CNS) lesions. HIV-infected patients, who present with a change in mental status or are found to have an abnormal neurologic examination, often are noted to have lesions, which can be detected by MRI or CT scan.[112] Toxoplasmosis is the most common opportunistic infection in AIDS patients, and the CNS is the most common site for this infection.[113] Malignant lymphoma also is one of the most common malignancies encountered in HIV-infected patients.[114] Tl-201 and Tc-99m sestamibi have been used to distinguish between these two complications in HIV-infected patients who present with intracranial mass lesions. Both agents have a sensitivity of close to 100% but a relatively lower specificity (54 and 69%, respectively).[115] Stereotactic brain biopsy has long been considered as the gold standard for the diagnosis of CNS lesions in AIDS, but it carries significant risks, and although it is the most specific technique, it is not very sensitive.[116] The role of PET in HIV-infected patients was first described by Hoffman et al[117] who studied 11 individuals with AIDS and CNS lesions and found FDG-PET imaging to be more accurate than CT or MRI in differentiating between a malignant (lymphoma, $n = 5$) and nonmalignant etiologies (toxoplasmosis, $n = 4$; syphilis, $n = 1$; progressive multifocal leukoencephalopathy, $n = 1$) for the CNS lesions. Malignant CNS lesions had a higher FDG uptake than nonmalignant. Using both a qualitative visual score and a semiquantitative count ratio by comparing the CNS lesion with contralateral brain, Heald et al[118] found that the CNS lesions diagnosed as lymphomas, had statistically higher visual scores ($P = 0.001$) and count ratios ($P = 0.002$) than CNS lesions diagnosed as infections. O'Doherty et al[46] showed that PET had an overall sensitivity and specificity of 92% and 94% respectively in the detection of infections or malignancies in patients with AIDS. This high specificity of FDG-PET can lead to initiating an early and an appropriate treatment strategy in these severely immunosuppressed patients.

Sarcoidosis

Sarcoidosis is a multisystem noncaseating granulomatous disease of unknown etiology. Correct assessment of disease activity is critical for initiating an optimal management plan because most patients will have a self-limited course whereas a small percentage may die without treatment soon after diagnosis. Several groups have reported FDG uptake by sarcoid granulomas,[15,53,119] which appear as typically active lymph nodes in the mediastinum and hilar regions (Fig. 5). By quantifying glucose metabolism in sarcoidosis, Brudin et al[15] has suggested that FDG uptake reflects likely disease activity and its extent at different stages of this unpredictable systemic disorder. Because lymph nodes harboring inflammatory and malignant cells appear with significant FDG uptake, this technique can not distinguish between sarcoidosis from diseases such as Hodgkin's or non-Hodgkin's lymphomas. However, FDG-PET is quite effective in assessing the extent and the degree of the disease after the initial diagnosis has been made.[120] Yamada et al[55] reported that by performing FDG and carbon-11 labeled methionine imaging, and by using the ratio of FDG to methionine in pretreatment evaluation, they were able to predict posttherapy course of the disease. Although in the group with an FDG/methionine ratio of greater than 2, the response rate was 78%, in the methionine dominant group it dropped to 38%.

Atherosclerosis

Atherosclerosis is the major cause of coronary heart disease, stroke, and peripheral vascular disorders.[121] Cardiovascular atherosclerotic disease involves mainly the aorta and arterial circulation of the heart, brain, kidneys, and limbs. Myocardial infarction, cerebral

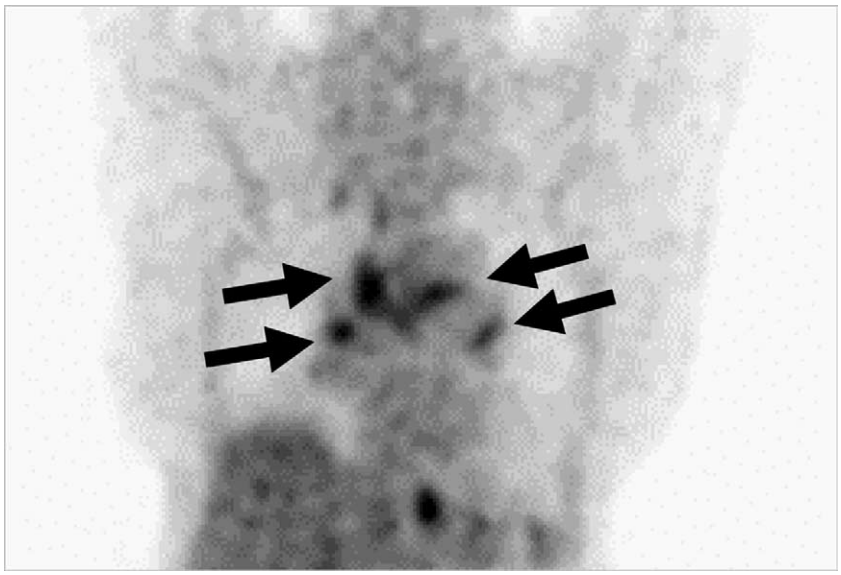

Figure 5 Coronal images of a 74-year-old female with hypercalcemia of unknown cause who was referred for a PET scanning to reveal a possible source of the finding. Bilateral hilar and mediastinal sites were seen on FDG-PET (see arrows), which were biopsied and were proven to be due to sarcoid.

infarction, renal failure and aortic aneurysms are the major consequences of this disease. Coronary heart disease is the number one cause of death in the United States and many other countries around the world. Initial lesions in atherosclerosis involve the intima of the arteries with the development of fatty streaks that may start in childhood.[122] Fatty streaks transform into atherosclerotic plaques by accumulation of connective tissue with an increased number of smooth muscle cells laden with lipids. More advanced lesions are later formed, which can become calcified.[123] Multiple factors contribute to the pathogenesis of atherosclerosis including dyslipidemia, endothelial dysfunction, inflammatory and immunologic factors, plaque rupture, and smoking. Inflammation is noted in the early histologic observations in the development of atherosclerosis.[124-126] Also in recent years there was much interest in the possibility that infections may cause or contribute to atherosclerosis. Recent publications have supported the role of *Chlamydia pneumoniae*,[127-129] cytomegalovirus,[130,131] and other infectious agents in initiating atherosclerosis.[132] Because FDG-PET has been shown to be able to detect a variety of inflammatory/infectious processes, it is logical to assume that this technique can also play a role in assessing atherosclerosis as an inflammatory process at the early stage disease, during its natural course and following therapeutic intervention.

It has been reported that there is a high correlation between the FDG uptake in the aorta and macrophage content of atherosclerotic lesions in an experimental rabbit model.[133] Our group has investigated the frequency of FDG uptake in the large arteries in relation to the atherogenic risk factors. We also have investigated whether FDG uptake of the large arteries is related to clinically known coronary artery disease. The presence of FDG uptake was assessed in 156 patients. The presence of FDG uptake was assessed in the abdominal aorta (AA), iliac (IA), and proximal femoral arteries (FAs) in 156 patients. Medical history of the atherogenic risk factors (age, cigarette smoking, hypertension, diabetes, high cholesterol, and obesity) and coronary artery disease (CAD) was identified for each patient. The frequency of vascular FDG uptake was compared between the patients without risk factors (group I, 23 patients) and those with at least 1 risk factor (group II, 133 patients). Vascular FDG uptake (Fig. 6) was present in 50% of the patients examined, and it correlated with old age. The correlation of each risk factor and known CAD with arterial FDG uptake was also assessed in the 3 different arteries. There was a significant difference in the frequency of FDG uptake between the 2 groups for the FA (22% versus 70%) and IA (30% versus 54%), but not for the AA (35% versus 53%). Among all risk factors, age was the most significant and consistent factor correlating with FDG uptake in all 3 arteries. Hypercholesterolemia also correlated consistently with FDG uptake in all 3 arteries. The correlation between the remaining risk factors and arterial FDG uptake was rather artery specific than consistent throughout all 3 arteries. A higher frequency of FDG uptake in the FA was seen in patients with CAD compared with those without CAD. Not all risk factors correlated with FDG uptake in different arteries. Among the risk factors, age and hypercholesterolemia most consistently correlated with FDG uptake in the AA, and the IA and proximal FAs. The

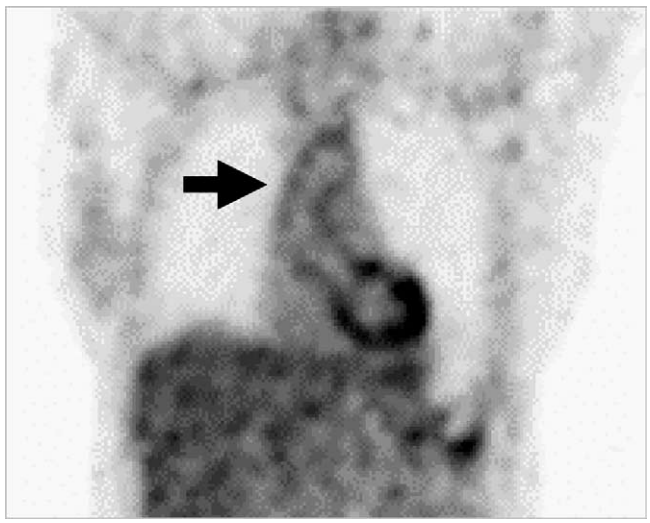

Figure 6 Aortic FDG uptake (arrow) in the thoracic aorta in a patient with severe atherosclerosis.

positive correlation of arterial FDG uptake with the atherogenic risk factors suggested a promising role for FDG-PET imaging in the diagnosis of atherosclerosis and follow-up after treatment intervention.[134] In an animal study using New Zealand White rabbits, Lederman et al[135] noted that by using a positron-sensitive fiberoptic probe it was possible to distinguish atherosclerotic from healthy artery. In a retrospective study Tatsumi et al[136] using PET-CT imaging compared the frequency of FDG uptake in the thoracic aortic wall and arterial calcification and reported that 50 of 85 patients had a least one area of metabolically active sites in the thoracic aortic wall. However, the FDG uptake did not correlate with the calcification sites seen on CT scan.

By measuring FDG uptake, we may be able to assess the degree of metabolic activity, possibly related to inflammation in the atherosclerotic arteries. FDG-PET imaging could help in the early detection of atherosclerosis, thereby affecting the management of high-risk patients, and monitoring response to treatment. Also, this technique could be utilized for determining the efficacy of therapeutic interventions that are currently adopted and the novel therapy that will be introduced in the future.

Vasculitis

Vasculitis is defined as the inflammation of the blood vessels with accumulation of leukocytes in the vessel wall and reactive damage to mural structures. The vasculitides are typically classified according to the size and type of vessels that most commonly are affected by the disorder.[137] PET has been reported to be useful in the diagnosis and treatment of patients with vasculitis as early as in 1987.[138] Blockmans et al[139] evaluated the use of FDG-PET in a series of 5 patients with polymyalgia rheumatica, 6 patients with giant cell arteritis, and 23 age-matched control subjects. An increase in FDG uptake was noted in the thoracic vessels in 4 of 5 patients with polymyalgia rheumatica, in 4 of 6 patients with giant cell arteritis compared with 1 of 23 control subjects ($P < 0.001$). Several reports have described increased FDG uptake in Takayasu arteritis, and have emphasized its value in detecting the extent of the disease in the body.[140,141] In a series of 15 patients with early aortitis (giant cell arteritis, n = 14; Takayasu arteritis, n = 1), Meller et al[142] compared FDG-PET and MRI for the initial diagnosis and following immunosuppressive therapy. The results of FDG-PET and MRI for the initial diagnosis were comparable, but FDG-PET detected more inflammatory vascular regions, and was more reliable in assessing disease activity following therapy than the latter modality. Webb et al[143] found that FDG-PET had a sensitivity of 92%, a specificity of 100%, and negative and positive predictive values of 85% and 100% respectively in the initial assessment of active vasculitis in Takayasu arteritis. Their conclusion was that FDG-PET could be used to evaluate the activity of the disease and to monitor the effectiveness of treatment. Balan et al[144] describe a patient in whom FDG-PET imaging was positive for widespread vasculitis, whereas In-111 white blood cell imaging was entirely normal. FDG-PET can detect Takayasu's arteritis in the early stages of this disorder.[140,143] The symptoms and signs at the early stage of Takayasu's arteritis is nonspecific, which may include fever, malaise, weight loss, arthralgia, and elevated erythrocyte sedimentation rate. The diagnosis of this disease is usually made by aortic arteriography at a relatively later stage. The early diagnosis of Takayasu arteritis with PET can allow early treatment, which may prevent progression to the later occlusive phase of the disease. It has been reported that when levels of FDG uptake in the vessels involved returned to normal following treatment there was a favorable outcome during the follow up period.[109,142] Based on the data presented, PET appears to have a great potential in the diagnosis and treatment of patients with vasculitis.

However, FDG-PET might not be sensitive enough to detect vasculitis of very small vessels. Horton's disease is a headache syndrome characterized by inflammation of the temporal and other cranial arteries. In a study performed by Brodmann et al[145] to determine the role of FDG-PET imaging as a non invasive technique for the diagnosis of Horton's disease, 22 patients with the clinical diagnosis of giant cell arteritis and a positive hypoechogenic halo in duplex sonography were examined with FDG-PET. All the patients who had positive sonographic signs in the large arteries (thoracic and abdominal aorta, and subclavian, axillary, and iliac arteries) had increased FDG uptake with complete agreement with the anatomical imaging results. However, FDG was false-negative in the blood vessels smaller than 4 mm. The authors concluded that PET is not suitable for the diagnosis of temporal arteritis and therefore cannot replace invasive biopsy for this purpose while FDG-PET is well suited for demonstrating giant cell arteritis in arteries exceeding 4 mm in diameter.[145]

Organ Transplantation

There are several potential applications of FDG-PET in the field of organ transplantation. FDG-PET is widely used in the diagnosis of cancer. It targets the metabolic activity of tumor cells, which is typically higher compared with normal cells. FDG-PET has been found to be highly accurate in the diagnosis of lung cancer, recurrent colon cancer, head and neck cancer, lymphoma, breast cancer, and melanoma.[146] It has the advantage of providing a whole body scanning within a reasonably short period of time. Malignancy either in organ donors or the recipients remains an absolute contraindication to transplantation. The cost of transplantation is very high, and the number of patients awaiting transplantation is increasing more rapidly than the number of transplant surgeries that can be performed annually.[147] Therefore, although FDG-PET is not a practical test for screening the general population for malignancy at this time due to its relatively high cost,[148] it has the potential to detect a wide variety of cancers unnoticed by other routine screening tests for potential organ recipients and donors, and can play a role in the pretransplantation planning. FDG-PET also has the potential to predict rejection. In an animal skin graft transplantation experiment, Heelan et al[12] demonstrated that rejected skin graft had significantly higher FDG accumulation than the nonrejected skin graft. It was reported that increased FDG accumulation of the transplanted heart might be an indicator of the rejection.[149] However, a later report indicated that glucose may be a preferred substrate in the normal functioning transplanted heart regardless the presence or the lack of rejection.[150] A recent report suggest that FDG-PET can help distinguish infection from rejection after lung transplantation and therefore this noninvasive and repeatable test could reduce the number of transbronchial biopsies required during episodes of respiratory failure after lung transplantation.[151] Posttransplantation lymphoproliferative disorder (PTLD) is a histologically heterogeneous disease that occurs in 4% to 8% of lung transplant recipients. Marom et al[152] have demonstrated that in patients with PTLD, there are foci of increased FDG accumulation, particularly in extrathoracic sites, that are not seen by conventional imaging techniques. Therefore, PET findings will allow more accurate staging of disease and thereby yielding useful prognostic information and guiding therapy in patients with PTLD.[152] Obviously, more investigation is necessary to define the potential role of this powerful methodology in the field of organ transplantation.

Plastic Surgery

Because FDG-PET reflects the metabolism in tissues, it can be used to assess the viability of surgical flaps in the immediate post surgical period. Smith et al[153] assessed FDG uptake in 30 patients after free-flap skeletal muscle transfer for closure of open wounds. They found that viable muscle flaps have significantly higher FDG accumulation than those that are nonviable and concluded that FDG-PET scanning can determine skeletal muscle viability in patients following free muscle flap transfer.[153] Similarly, Aigner et al[154] performed a study in 38 patients who had oro-maxillo-facial flaps. The patients had an FDG-PET scan at 3 to 7 days after surgery. The patients who had no photopenic defects had a favorable outcome (23/38). The patients who had small defects in their flaps had a delayed but uncomplicated healing process (n = 13/28). Three patients who had a large photopenic defect demonstrated by PET were noted to have early necrosis.

Muscle Uptake

Kostakoglu et al[155] first reported FDG uptake by the laryngeal muscles secondary to activation of the patient's vocal folds and related laryngeal muscles during speech. In their study, they found that patients who spoke continually during the uptake period had high-grade FDG uptake, those who spoke intermittently had low-grade uptake and those who remained silent had no detectable increase in FDG uptake in the region of the larynx.

FDG uptake in the skeletal muscle is often seen in the trapezius, sternocleidomastoid, paraspinal and diaphragmatic muscles. Muscular uptake can usually be distinguished from malignant disease because it is often symmetric and matches the anatomy of muscular groups. With the advent of PET/CT, FDG activity in the neck and shoulders was found to be also present in the adipose tissue and was attributed to brown fat uptake.[156,157] The use of benzodiazepines before FDG injection might be useful in selected patients,[158] but it is not necessary on a routine basis. It is important that the patient stays in a relaxed resting state before and after the injection of FDG in most studies to avoid undesirable muscle FDG uptake.

In patients with chronic obstructive pulmonary disease, excessive contraction of accessory muscles is required to facilitate expiration therefore the uptake in the intercostal muscles increases[59] and should not be misinterpreted as ribs metastases or bone marrow uptake. Hyperventilation may induce uptake in the diaphragm as well. We recently investigated changes in metabolic activity of the soft tissues surrounding the lumbar spine in patients with a history of low back pain (LBP). We were specifically interested in investigating muscle spasm as the cause of LBP in this population. The patients were given a detailed questionnaire regarding LBP and other related medical history before the administration of FDG. The patients presented for a PET scan predominantly for the evaluation of known or suspected malignancies. A total of 43 patients returned completed questionnaires. A total of 8 patients demonstrated nonspecific mildly increased FDG activity in the region of the soft tissues and spinous processes of the lower thoracic and lumbar spine (3 patients with both acute and chronic LBP; 4 patients with chronic LBP but no acute symptoms at the time of the PET scan; 1 patient with no history of either acute or chronic LBP). Only in 1 patient with acute and chronic pain extending from the lower lumbar spine to the left hip, increased right psoas muscle uptake was observed in this population. The predominant finding in our study was mildly increased FDG activity in the soft tissues superficial to the lumbar spine. No intense FDG activity was present in the lower back musculature of patients with either acute or chronic LBP. Therefore, muscle spasm as the cause of LBP may be overestimated as a common occurrence in this population. Thus, routine administration of muscle relaxants may not be scientifically justified. FDG-PET may play a role in differentiating the patients who have muscle spasms and LBP (and possibly musculoskeletal system elsewhere in the body) and could benefit from muscle relaxants from those without and therefore avoid administrating these drugs unnecessarily for the latter group.

Several groups have used FDG-PET in the evaluation of muscle metabolic activity in different situations. Tashiro et al[159] performed FDG-PET on 7 healthy male runners after running and compared the PET images from 7 resting controls. They found that the highest metabolic activation was in the posterior compartment of the leg, whereas thigh muscles showed relatively little changes during running. They concluded that whole-body FDG-PET is a useful tool for the investigation of muscular activity during exercise. In a different investigation involving 17 subjects, Oi et al[160] demonstrated that the muscular activity of the soleus was highest among all the muscles examined after subjects walking. Pappas et al[161] conducted PET and FDG uptake measurements in the skeletal muscles in 17 subjects who just performed either elbow flexion, elbow extension, or ankle plantar flexion. They found that differences in relative FDG uptake could be demonstrated as exercise tasks and loads were varied, permitting differentiation of active muscles. They concluded that FDG-PET is capable of characterizing task-specific muscle activity and measuring intramuscular variations of glucose metabolism within exercising skeletal muscle.[161] The rotator cuff is a group of 4 muscles. Rotator cuff tears account for almost 50% of major shoulder injuries but are sometimes difficult to diagnose.[162] Prevalence of rotator cuff tear increases with age from less than 5% for subjects in their twenties to more than 80% for those in their seventies. Shinozaki et al has used PET/MRI fusion to analyze the affected rotator cuff muscle activity.[163] It is conceivable that in the near future, PET will play a bigger role in the evaluation of muscle activity and muscle injuries in exercise and age related disorders (Fig. 7).

Inflammatory Bowel Disease (IBD)

PET has been reported to be useful in detecting disease activity in patients with IBD.[164-166] However, normal FDG uptake in the bowel varies in distribution and intensity due to several factors[167,168] and can affect the sensitivity and specificity of this technique in this disorder. Despite these disadvantages, FDG-PET can play a major role in the evaluation of IBD in the pediatric population, since we have noted that FDG uptake in the abdomen is affected by age, and the pediatric population has low FDG activity in the bowel. Therefore, in this specific age group, bowel activity is unlikely to interfere with the interpretation of the disease activity. In a new method which utilized FDG-labeled WBC to image inflammation, a good correlation was noted between the degree of inflammation and the level of FDG uptake in patients with IBD and therefore this approach could be used for quantitative assessment of bowel disease noninvasively.[169]

Pneumoconioses

Occupational pneumoconioses are incurable lung diseases caused by the inhalation of noxious substances encountered in the workplace, which are responsible for more than 3000 deaths in the United States each year. Pneumoconioses include coal worker's pneumoconiosis, silicosis, asbestosis, and berylliosis. Silicosis and asbestosis are the two major types of pneumoconiosis. These diseases may be progressive even after dust exposure has ceased.[170] Dust reduction measures in the coal mines, as well as the improvement in exposure-prevention measures, have reduced the coal dust-

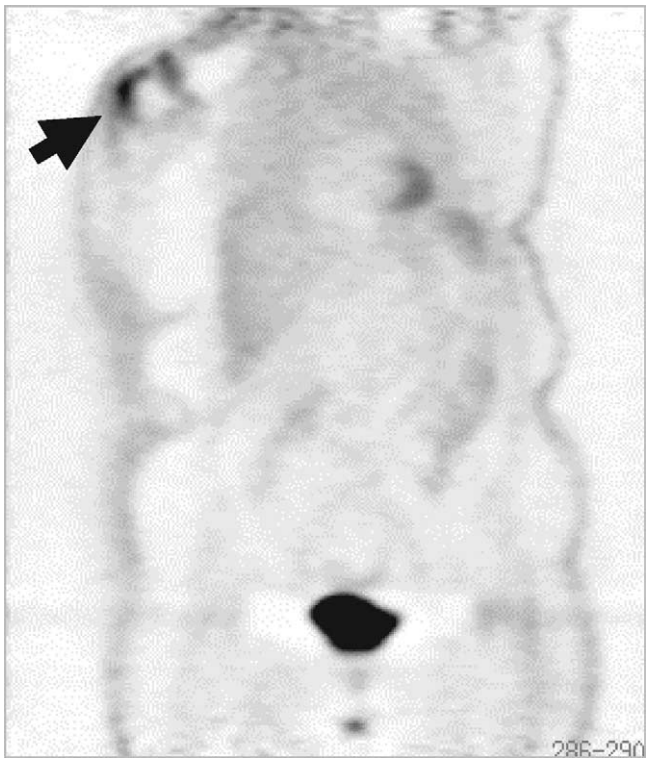

Figure 7 Coronal images of a 64-year-old female with rotator cuff tear of the right shoulder. Increased FDG uptake (arrow) around the glenohumeral joint due to inflammation.

induced disease. Silicosis is caused by the inhalation of free silica particles that activate the macrophages to secrete cytokines mediating an inflammatory reaction and inducing fibroblasts proliferation and collagen deposition.[171] Silica causes the activation and release of mediators by the macrophages such as interleukin-1, tumor necrosis factor (TNF), fibronectin, lipid mediators, oxygen-derived free radicals, and fibrogenic cytokines. Intratracheal instillation of bleomycin or silica in mice causes a significant increase in the lung hydroxyproline.[172] Asbestos, like other inorganic dusts, activates lung macrophages and causes the release of chemotactic factors and fibrogenic mediators. In contrast to other pneumoconioses, cigarette smoking in asbestos workers increases the incidence of lung carcinoma, and the lifetime risk to asbestos workers of developing malignant pleural mesothelioma is about 8%. There were several reports of increased FDG lung uptake in patients with pneumoconiosis.[173,174] There is variable degree of FDG uptake in the lungs of patients with coal worker's pneumoconiosis, silicosis, and active fibrosis. FDG uptake in these patients is nonspecific and could be related to the activation of inflammatory cells as well as fibroblasts.

FDG-PET imaging have demonstrated increased uptake in pneumoconiosis.[173,175] Progressive massive fibrosis often demonstrates significantly increased FDG accumulation. This increased uptake is likely related to not only fibroblasts but also inflammatory cells. A specific radiotracer that may selectively localize in the fibroblasts and not in the inflammatory cells would be an appropriate approach for the diagnosis of pneumoconiosis such as silicosis with active fibrosis. Currently these conditions usually are diagnosed in late stages, when therapeutic intervention may not be effective. PET imaging with 18F-fluoroproline offers the possibility of providing early and specific diagnosis of this often-debilitating disorder. In a preliminary study in animal model of induced silicosis, Wallace et al[176] demonstrated that there was significantly higher fluoroproline uptake in the lungs of silica-challenged rabbit as compared with a control group. Wilcoxon rank-sum tests found significantly higher uptake by the silica-challenged animals at 1, 2, 4, and 5 months, with respective P values of 0.0001, 0.001, 0.02, and 0.03. There was a statistically significant relationship between PET imaging scores and fibrosis scores for silica-challenged animals. The correlation coefficients in the right and left lungs were 0.51 ($P = 0.03$) and 0.66 ($P = 0.003$), respectively, and higher fibrosis scores were observed as fluoroproline/PET scores increased.[176] There is extensive literature on animal models of silicosis in which autoradiographic analysis revealed tritiated or 14C-labeled proline uptake at the alveolar interstitial sites of fibroblast collagen synthesis; this suggests that a major fraction of the proline analog is taken up as a result of collagen synthesis. A definitive answer may require either a biochemical assay of the fractional amount of fluoroproline sequestered in the lungs as procollagen or an autoradiographic study of the microanatomic location of the accumulated fluoroproline. Such research studies will determine whether the compound is in the pulmonary interstitial fibroblasts or in the alveolar inflammatory cells as a consequence of inflammatory reaction.

Pleural Diseases

A pleural sac formed by a parietal pleura (lining the outer surface of the chest wall) and a visceral pleura (lining the inner surface of the lung) separates each lung. The pleural cavity is a closed potential space that has a negative pressure and normally contains a thin layer of approximately 5 to 15 mL of clear serous fluid. Pathologic involvement of the pleura is caused by a variety of inflammatory, noninflammatory and malignant diseases. Primary disorders of the pleura include primary intrapleural bacterial infection, and primary neoplasm of the pleura (mesothelioma). Pleural effusion is usually a secondary complication of an underlying disease. Pleural effusion is a common manifestation of both primary and secondary pleural involvement and is divided into inflammatory and noninflammatory.

Diagnostic thoracentesis and biochemical and cytological tests are very helpful in establishing the cause of effusion but have a low yield in malignant effusion. Imaging the pleural fluid relies on the facts that the pleural fluid gravitates to the dependent areas in the thoracic cavity and that the lung lobes maintain their shape during collapse. A chest x-ray is the first modality used in the evaluation of pleural disease but has a low sensitivity and specificity. Ultrasound examination is a fast, easy, low-cost method to detect, locate, and characterize pleural effusion. It can differentiate between effusion and pleural thickening and between effusion and subphrenic fluid collection. It can also provide guidance for thoracentesis.

Conventional chest radiograph is the first imaging modality used to evaluate a pleural disease, but it has a low sensitivity and specificity, especially in upright chest radiographs, with a better sensitivity in decubitus radiographs.[177] Ultrasonography permits easy identification of free or loculated pleural effusions. It is an easy, lost cost-method that can differentiate loculated effusions from solid masses, and guide thoracentesis. CT scan is considered the best modality to evaluate pleural disease and visualize the pleural space. Excellent anatomic delineation leads to the distinct visualization of the location, extent, and margins of the pleural abnormality and evaluation of underlying lung parenchyma. However, many infectious disorders, such as tuberculosis or empyema, can cause fibrotic changes, which cannot be differentiated from pleural malignancies on anatomic imaging. The sensitivity and specificity of CT to predict the malignant nature of diffuse pleural lesions are low. CT scan cannot differentiate between benign and malignant pleural disease.

MRI, because of cardiac and respiratory motion artifacts, has limited value in evaluating pleural disease but can differentiate between benign fibrous mesothelioma (low signal intensity on T_2-weighted images) and malignant mesothelioma (high signal intensity).[178]

Although pleural fluid cytology has a better diagnostic yield than needle biopsy, the combination yields a sensitivity of less than 40%. Needle biopsy is associated with the risk of pneumothorax, tumor seeding, and bleeding. Thoracoscopy is the procedure of choice for the diagnosis and management of neoplastic diseases of the pleura. It provides direct visualization of the pleural space and the abnormalities within this anatomic compartment. Tissue sampling and pleurodesis can be performed with the procedure. This modality is, however, limited mainly by its availability, cost, expertise, and postprocedure chest tube placement with video-assisted thoracic surgery. Complications include tumor seeding along the chest wall, persistent air leaks, hemorrhage, subcutaneous emphysema, and wound infections. Open biopsy provides the best visualization of the pleural space and is the modality of choice for the investigation of pleural disease undiagnosed by the previously mentioned methods. However, because of the complexity, invasiveness, and costs, it has slowly been replaced by thoracoscopy. However, thoracoscopy is expensive and also has some complications that include a persistent air leak (more than 7 days) in 2% of cases, subcutaneous emphysema in 2% of cases, and postoperative fever in 16% of cases.[179,180]

FDG-PET is a noninvasive imaging modality that is often used as an effective modality in the management of patients with lung cancer and variety of other cancers. Increased glucose uptake and metabolism by neoplastic cells is the basis of this functional imaging technique in the investigation of a variety of malignant disorders. Apart from cancers, PET has also proven useful in the diagnosis and treatment of infections and inflammation in different tissues. There is convincing evidence for the usefulness of PET in the diagnosis and staging of malignant mesotheliomas, but this modality has not yet been evaluated for its use in other pleural diseases. Normally there is minimal FDG uptake in the pleura, which cannot be separated from uptake in the chest wall.[181] Direct comparison with the CT scan requires transaxial FDG-PET images, but the use of other planes allows detailed analysis of various anatomic sites. Because the patient is in the supine position when the images are acquired, the pleural fluid gravitates to the posterior part of the lungs, and this should be taken into consideration in the interpretation of these scans.

Asbestos-Related Pleural Disease and PET

Exposure to asbestos leads to a spectrum of lung parenchymal and pleural pathologies with distinct clinical features that require complex management strategies. Asbestosis is characterized by chronic parenchymal lung fibrosis and visceral pleural thickening and results in an increased risk for lung and pleural malignancies. Pleural plaques are smooth, raised, irregular lesions on the parietal pleura in the lateral and mid lung zones. They are the most frequent manifestations of asbestos exposure and are usually seen as an incidental finding on a chest x-ray but are better characterized by CT. Pleural fibrosis and viscero-parietal reaction are characterized by diffuse or localized thickening of the pleura. Benign asbestos-related pleural effusion has a good prognosis and is not a precursor for the development of mesothelioma but frequently requires thoracoscopic biopsy to rule out malignancy. Benign fibrous mesothelioma is a rare, nonmalignant, localized tumor of the pleura that is not related to asbestos exposure and can be cured by excisional surgery. It is thus very important to differentiate benign lesions of the pleura from malignant mesothelioma, which is also a relatively rare but has a very poor prognosis.

Malignant mesothelioma is predominantly a disease of men, and patients have a mean age of 60 years at the time of diagnosis. In the United States, more than 2000 individuals are diagnosed with this cancer every year. The risk of developing mesothelioma in an individual with occupational asbestos exposure is approximately 10% over a lifetime. Patients usually present with a unilateral pleural mass and pleural effusion first seen on chest x-ray. More than 50% of the patients have pleural effusion at the time of diagnosis, but cytology of pleural fluid is positive only in approximately 25%. Distant metastasis occurs very late. The median survival for patients with mesothelioma after diagnosis is from 12 to 18 months. The radiologic appearances of benign and malignant pleural disease are very similar. Definitive diagnosis is currently made by thoracoscopic biopsy, which carries the risk of seeding the operative tract. CT is not specific for the diagnosis or mediastinal staging, but CT, along with thoracoscopy, is currently used for staging and restaging. MRI does not provide additional information compared with CT scan in patients with unresectable disease. Local extension into the mediastinum and hematogenous dissemination are the markers for unresectable disease, which is treated with combined aggressive modality therapy.

Several studies[182-184] have shown that FDG-PET can accurately determine whether there is malignant transformation of reactive pleural disease and can identify the sites of involvement by the process, and as such it is clearly superior to CT in staging of the disease.[181,185,186] These studies have compared FDG-PET with CT, mediastinoscopy, thoracoscopy, and pathologic examination. Mesothelioma is seen as a linear area of intense FDG uptake surrounding the lungs.[187] Benard et al[188] studying 28 consecutive patients suspected of having malignant mesothelioma, reported very high sensitivity and specificity of FDG-PET in that a sensitivity of 91% and specificity of 100% could be achieved for differentiating benign from malignant disease by using a cutoff SUV of 2.0. They reported an excellent correlation of FDG-PET findings with thoracoscopy in 16 of 18 cases with malignant disease. Lymph node involvement was noted on FDG-PET images in 12 patients, 9 of which appeared normal on CT scans. In a similar study, Schneider et al[185] showed FDG uptake in all of 18 patients with primary mesotheliomas. Overall, FDG-PET could identify the presence or absence of metastatic disease in 89% of the patients. By accurately identifying the involvement of mediastinal nodes or extrathoracic sites, FDG-PET could improve patient selection for combined-modality treatment. On the basis of FDG-PET Schneider et al excluded 2 patients from surgical therapy and noted 2 false-positive lesions in 18 patients. Comparing FDG-PET with CT in 8 patients with malignant mesothelioma, Zubeldia et al[186] noted that FDG-PET upstaged 2 patients from localized to widespread disease and downstaged 1 patient. They also concluded that FDG-PET was more accurate than CT in staging of patients with mesothelioma. FDG-PET has thus been shown to better identify the extent of disease, stage the disease in the mediastinum, evaluate abnormal findings in the contralateral lung, and detect occult extrathoracic metastasis. Schneider et al also found that the mean SUV in 18 mesothelioma patients was 7.6. Benard et al noted that mesotheliomas of the epithelial subtype had lower levels of FDG uptake (SUV, 3.78 ± 1.96; $n = 9$) than the mixed or sarcomatoid subtype. They also showed that patients with highly active mesotheliomas on FDG-PET imaging have a poor prognosis. High FDG uptake in these tumors indicates shorter patient survival.[189]

These results call for the routine use of FDG-PET for differentiating benign from malignant pleural thickenings and for the diagnosis

and staging of pleural mesothelioma. FDG-PET can provide a semiquantitative index of disease activity that may be used to monitor the response to clinical or experimental therapeutic regimens. Thoracoscopy, for definitive diagnosis, can be guided by FDG-PET to identify the best sites for the purpose of achieving high yields from such invasive procedures.

The Role of PET in Characterizing the Nature of Pleural Effusion

Pleural effusion is frequently noted in a variety of benign and malignant disorders that affect this structure and adjacent anatomic sites. Accurate characterization of the process is of the utmost importance in the management of these patients. Two hundred thousand individuals are diagnosed with malignant pleural effusions every year in the United States. Most effusions secondary to metastasis are from lung, breast, gastric, and ovarian cancers and lymphomas. Approximately 50% of patients with metastasis to the pleural metastasis to the pleura will develop effusion. The prognosis in patients with malignant pleural effusions is very poor, and current treatment options include chemotherapy and pleurodesis. Pleural effusions are common in patients with lung cancer. Many of these are benign and may represent reactive fluid collections. As many as one third of patients with lung cancer will have pleural metastasis at the time of presentation. A recent study has shown that patients with lung cancer and benign pleural effusion have better survival than those with stage IV disease and biopsy-proven malignant effusion.[190] In the presence of malignant pleural effusion, the lung cancer is considered unresectable. Similarly, it is very useful to determine a benign underlying etiology for an effusion to prevent delays in the surgical treatment of resectable lung cancer. It is thus very important to differentiate between benign and malignant pleural effusions. CT scan is used extensively for the evaluation of pleural disease but has been shown to be incapable of differentiating benign from malignant pleural disease and fibrosis from residual tumor after therapy.[191]

Data from several recent reports indicate that benign pleural plaques or inflammatory conditions can be successfully differentiated from malignant pleural involvement, on the basis of the degree of the FDG uptake in the pleura.[192] These studies have shown high sensitivity and accuracy in differentiating benign from malignant pleural disease.[193-195] In a study by Gupta et al,[192] FDG-PET accurately classified 32 (91.4%) of 35 patients. FDG-PET was found to have a sensitivity of 88.8%, a specificity of 94.1%, and a predictive accuracy of 91.4% for detecting malignant pleural effusion from metastatic pleural involvement. The positive predictive value of FDG-PET was 94.1%, and the negative predictive value was 88.8%. FDG-PET did not show significant uptake in benign pleural effusion cases except in 1 of 17 patients, in whom only mild FDG uptake was seen. In particular, patients with acute bacterial pneumonias with inflammatory pleural effusion showed no or only mild pleural uptake, which further diminished on follow-up studies. Accuracy of FDG-PET in the study was greater than pleural fluid cytology. In a recent study, we evaluated 106 cancer patients in whom the degree of FDG uptake was examined in the pleura. On the basis of the history, findings on the PET scan, the SUV of the pleural uptake, clinical follow-up, and biopsies, the patients were classified as having benign/inflammatory (n = 25) or malignant (n = 81) pleural disease. We noted that the average SUV of the malignant pleural lesions was 4.18. Review of the recent CT scan showed evidence of pleural disease in only 60% of patients with malignant pleural disease and in 64% of patients with benign pleural disease. Sensitivity and specificity for malignant pleural disease were, respectively, 90% and 72%, with an SUV threshold of 2.0. In 9 patients, direct extension of the FDG activity into the pleura from the primary lung lesion was noted on PET; in only 3 (33%) was such evidence seen on the CT scan.

The causes of detectable FDG uptake in nonmalignant pleural disorders include asbestos reaction, pleural effusion secondary to inflammatory process, pleurisy, recent surgery, and radiotherapy. Benign inflammatory processes (eg, tuberculosis and parapneumonic effusion) can cause increased activity in the pleura with an SUV of more than 2.5. Potential causes of false-positive FDG-PET studies include sarcoidosis, tuberculosis, fungal infections, acute fractures, skeletal muscle trauma, and bacterial infections. Patients with pleural disease undergoing PET scan should therefore be asked about a history of any surgical procedures such as lobectomies, thoracoscopies, and thoracentesis; infections such as pneumonia or tuberculosis; symptoms of chest pain; shortness of breath; history of congestive heart failure; and renal or hepatic failure, which all can cause benign pleural effusion. Finally, when reviewing the PET images, they should be compared with recent CT scans or reports from other investigations, such as biopsies, MRI, and recent chest x-ray.

We conclude that FDG-PET can be used for differentiating benign and malignant pleural disease. FDG-PET can identify other occult foci of metastasis or even a primary tumor in patients with malignant effusions and an unknown primary tumor. FDG-PET may provide a useful alternate diagnostic method to invasive tests especially in those with equivocal findings on CT or negative results from pleural cytology after thoracocentesis. Evaluation with FDG-PET could reduce the number of open pleural biopsies and thoracotomies performed for benign pleural disease. Dual time point imaging may also have a role in the evaluation of pleural diseases by FDG-PET. We also believe that seeding of the pleura with malignant cells and, thereby, changes in the FDG metabolism precede anatomic changes, and therefore pleural involvement by malignant disease and even direct extension can be diagnosed earlier with a PET scan than with anatomic imaging techniques.

Thymus Hyperplasia

Normal physiological thymus activity is frequently observed in children and in some young adults.[196,197] Increased FDG activity in the thymus is also noted in thymus hyperplasia following chemotherapy.[198] FDG-PET uptake in the thymus has been reported secondary to radioiodine therapy[199] (we have noted several cases in this setting), which is attributed to radiation-induced inflammation of the gland. In another report, thymus hyperplasia occurred 5 months after autologous peripheral blood stem-cell transplantation in a 31-year-old patient with anaplastic large cell lymphoma.[200]

Hardy et al[201] noted, in a case study, thymic reconstitution by FDG-PET in a patient with HIV-1 infection who was treated with highly active antiretroviral therapy, which may provide a potential role in evaluating such treatment. FDG-PET thus can monitor restoration of thymic function necessary for long-term immunocompetence and protection against opportunistic infections. The restoration of the immune response as detected by thymic reconstitution using FDG-PET may be employed for unnecessary prophylactic therapies in immunosuppressed patients.

Thyroiditis and Thyroid Nodule

Several reports of FDG uptake in the thyroid gland have attributed the uptake of this agent to thyroiditis.[61,202] In a reported case of Riedel's thyroiditis and retroperitoneal fibrosis, there was an increase in FDG uptake by the thyroid gland, which decreased after treatment with steroids was initiated. In this report, the uptake by

the thyroid gland was attributed to active inflammation involving lymphocytes, plasma cells, and fibroblast proliferation.[203] In another case report, diffusely increased FDG uptake by the thyroid gland was proven to be related to Hashimoto's thyroiditis that mimicked thyroid cancer.[204] Uematsu et al[202] studied 11 patients with nodular thyroid gland which were imaged with FDG-PET and thalium-201 before surgery. Four patients were found to have a differentiated papillary carcinomas, 5 were diagnosed with benign follicular adenomas, 1 suffered from a multinodular goiter, and the last had chronic thyroiditis. FDG uptake increased over time in the malignant tumors, whereas in the benign nodules the reverse was observed. Increased FDG uptake by the thyroid gland has also been reported in a patient with Grave's disease.[205] This is due to increased metabolism of the hyperactive thyroids cells. Focal uptake has a high likelihood of being associated with a malignant process and should be further evaluated.[206]

By now it is known that FDG uptake correlates well with the serum TSH levels. In vitro cell culture experiments have demonstrated that incrementally increase in the thyroid-stimulating hormone (TSH) levels in an in vitro setting, significantly, increased the FDG uptake in a time- and concentration-dependent manner: thyroid cells cultured at a TSH concentration of 50 muU/mL compared with those in a TSH-free medium took up double the amount of FDG.[207] Also uptake with TSH preincubation was approximately 300% of that of TSH free medium at 72 h.[207] Clinical studies suggest that FDG uptake in the recurrent and metastatic thyroid carcinoma also depends on the TSH levels.[208-210] Conceivably, diffuse thyroid FDG uptake in the gland without history of other known thyroid disorder might be caused by increased TSH levels and may therefore indicate hypothyroidism. As such the possibility of subclinical hypothyroidism should be raised in patients with diffuse thyroid uptake and without symptoms of hyperthyroidism.

Joints

Increased FDG uptake is frequently seen around various joints, mostly around the glenohumeral, hip, acromio-clavicular, and talotibial joints. The accumulation of FDG around these joints is likely due to inflammation of the synovial tissue surrounding the joints.[211] Palmer et al[212] conducted a study on 12 patients with wrist inflammation who were receiving antiinflammatory therapy and the response was assessed by using MRI and PET. The patients were imaged off medications for 2 weeks, then after 2 weeks of treatment with prednisone or nonsteroid antiinflammatory drugs, and after 12 weeks of treatment with methotrexate. There was close correlation between volume of enhancing pannus from fat-suppressed MR images and FDG uptake ($P < 0.0001$), as well as the changes over time of volume of enhancing pannus and SUV ($P < 0.0002$). These data support the possible role that PET may play in assessing the degree of joint inflammation and determining the efficacy of antiinflammatory drugs. Roivainen et al[213] compared (11)C-choline and FDG PET imaging with MRI in 10 patients with inflammatory joint disease and clinical signs of inflammation. All the patients showed high accumulation of both (11)C-choline and (18)F-FDG at the site of arthritic changes with a mean SUV of 1.5 ± 0.9 g/mL ($n = 10$) and 1.9 ± 0.9 g/mL ($n = 10$), respectively for choline and FDG ($P = 0.017$). However, the kinetic influx constant was 8 times higher for (11)C-choline. Both radiotracers correlated highly with the volume of the inflamed synovium. One of the potential roles for PET is to provide quantitative information on the degree of inflammation in the joints, which will affect the management of patients with rheumatologic diseases. PET may allow monitoring the response to antiinflammatory drugs. Since many of these drugs have serious adverse effects and administration to patients with chronic inflammatory diseases who require multiple treatments over an extended period of time, accurate assessment of response by PET may add a major dimension to such therapy.

We retrospectively reviewed the FDG-PET images of the lower extremities of 40 patients who presented for the evaluation of a variety of medical conditions. The purpose of this retrospective study was to determine normal patterns and changes with normal aging that occur in the FDG uptake of the lower extremities using SUV. The increase in SUV in the knees and hip joints correlated positively with patient's age. This may be a result of subclinical inflammatory synovial proliferation or other chronic inflammatory processes, which occur in aging joints such as degenerative joint disease.

Clot Detection

Although the current noninvasive imaging tests used for the detection of clot formation are readily available and are associated with minimal morbidity and cost, they may be less accurate than invasive techniques especially in difficult anatomic sites. There exist few reports in the literature about the detection by FDG-PET of clots in abdominal aorta, aortic aneurysm, superior vena cava, and deep venous thrombosis.[214-217] We have retrospectively reviewed the whole body FDG-PET images of 19 patients who had confirmed thrombosis based on followed studies and outcome. The findings on PET images were correlated with the clinical course, radiological examinations, and other pertinent information. Focal sites of increased FDG activity correlated with the following diagnoses: septic thrombophlebitis (9 patients), complicated vascular grafts (4 patients), spontaneous clot formation (3 patients), and catheter-related thrombosis (3 patients). The mean SUV in clots was 4.4 with a standard deviation of 2.0. The mechanism of FDG uptake in blood clots is still not fully understood. The presence of inflammatory cells in the sterile as well as infected clots may play a factor. These preliminary data demonstrate that FDG-PET imaging can visualize clots at different anatomic sites. However, in vitro and animal studies are required to evaluate the sensitivity and specificity of FDG-PET in clot detection and the underlying biological factors that are responsible for this observation.

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