FDG PET Assessment of Osteomyelitis: A Review

Phyllis Dioguardi, MD, MA[a,*], Santosh R. Gaddam, MD[a], Hongming Zhuang, MD, PhD[b], Drew A. Torigian, MD, MA[c], Abass Alavi, MD, PhD (Hon), DSc (Hon)[a]

KEYWORDS

- FDG-PET • PET/CT • Osteomyelitis
- Musculoskeletal infection • Radionuclide imaging
- Chronic osteomyelitis • Prosthesis-related infections
- Complicated diabetic foot

The ability to identify infection quickly and accurately is a major goal of diagnostic medicine because, despite greater understanding of how infection is caused and how it evolves, it remains a major source of patient morbidity and mortality worldwide. Early diagnosis and exclusion of infection and inflammation are of the utmost importance for optimal management of patients with infections such as osteomyelitis. Despite important advances in surgical and long-term antibiotic treatment, it often remains refractory to therapy, leading to chronic illness. The diagnosis of chronic infection may be difficult, because signs and symptoms may be absent. Because the infection often develops in an indirect manner and threatens to relapse, the diagnosis of posttraumatic/postsurgical osteomyelitis is usually made from a combination of clinical, laboratory, and imaging examinations. Together with the involved clinician, surgeon, microbiologist, and pathologist, the radiologist and nuclear medicine physician have to make use of all available information to exclude or confirm the presence of active infection or further complications of the disease.[1]

Imaging plays an increasing role in the care of patients with infectious and inflammatory diseases. Structural imaging such as plain film radiography, computed tomography (CT), and magnetic resonance (MR) imaging is most commonly used to detect and localize structural changes that have developed because of infection and inflammation. More recently, functional and molecular imaging methods have been developed (eg, [^{18}F]fluorodeoxyglucose [FDG] PET) that are complementary to structural imaging modalities and are proving effective in guiding the care of patients with infectious and inflammatory disorders. Nuclear medicine has for a long time focused its attention on the use of molecular imaging to enhance the rapid and accurate identification and localization of infections (particularly osteomyelitis) that may occur following trauma, in association with joint prosthesis, or in the feet of patients with diabetes mellitus. Several molecular imaging agents are already in clinical use, including labeled antibacterial agents, labeled antimicrobial peptides, monoclonal antibodies for leukocyte labeling, and labeled liposomes. Foremost among these imaging agents is FDG, which has been touted as the molecule of the millennium.

FDG-PET has an established record of efficacy in the assessment and detection of a variety of

[a] Division of Nuclear Medicine, Department of Radiology, Hospital of the University of Pennsylvania, 3400 Spruce Street, Philadelphia, PA 19104, USA
[b] Division of Nuclear Medicine, Department of Radiology, The Children's Hospital of Philadelphia, University of Pennsylvania School of Medicine, 34th Street and Civic Center Boulevard, Philadelphia, PA 19104, USA
[c] Department of Radiology, Hospital of the University of Pennsylvania, 3400 Spruce Street, Philadelphia, PA 19104, USA
* Corresponding author.
E-mail address: phyllis.dioguardi@uphs.upenn.edu

PET Clin 7 (2012) 161–179
doi:10.1016/j.cpet.2012.01.011

nononcologic disease conditions. The diagnosis of infection and the ability to distinguish bacterial infection from nonbacterial inflammation through the use of PET has gained interest in recent years. With modern advances, FDG-PET is becoming a more widely accepted modality for identifying a diverse group of infectious and inflammatory processes, such as osteomyelitis, prosthesis-related infections, spondylodiscitis, sarcoidosis, and infections related to acquired immunodeficiency syndrome(AIDS), and is useful for the evaluation of patients with fever of unknown origin (FUO). However, FDG and other radionuclide imaging agents target components of these inflammatory responses, none of which are infection specific. In spite of the success of FDG-PET in oncology, the test is not specific for malignancy. FDG-PET is a method to identify cells and tissues with an increased metabolic (glycolytic) rate. Because accelerated energy metabolism is not specific to cancer, many noncancerous tissues take up FDG, and false-positive findings are common. Consequently, This article provides a survey of the most important current applications of FDG-PET in osteomyelitis and notes the specific technical and/or diagnostic challenges in any given application.[2]

RADIOTRACERS

Radiotracers for the detection and localization of infectious and inflammatory processes have been used since the 1950s. The radiotracers used to diagnose bone infection are divided into 2 groups: the first group comprises infection/inflammation seeking agents, which include ^{67}Ga, radiolabeled antigranulocyte antibodies, and radiolabeled leukocytes for white blood cell (WBC) scintigraphy; the second group contains agents that reflect metabolic changes associated with infection/inflammation, such as radiolabeled diphosphonates for bone scintigraphy. The introduction of radiotracers in nuclear medicine has enhanced infection imaging, because they depend on the demonstration of pathophysiologic changes, which occur earlier in the infectious process and also resolve quickly after cure of the infection compared with gross anatomic changes in osseous structure as detected by conventional imaging modalities. Ideally, radiotracers developed for the detection of infection and inflammation should be highly sensitive and able to distinguish between infectious and noninfectious inflammation. Recently, a wide variety of radiotracers have been tested for imaging infectious and inflammation processes in the hopes of achieving the desirable characteristic of high specificity. Currently, there are only a few agents in use for infection and inflammation imaging. These agents include FDG, autologous WBC labeled with ^{99m}Tc-hexamethylpropylene amine oxime or ^{111}In-oxine, ^{99m}Tc-labeled diphosphonates such as methylene diphosphonate (MDP) or hydroxymethylene diphosphonate, ^{67}Ga-citrate, ^{99m}Tc-labeled nanocolloids, and ^{99m}Tc-labeled or ^{111}In-labeled proteins, such as immunoglobulin (Ig) G or albumin. The main limitation of these techniques is lack of specificity, because these methods target/label components of the inflammatory response itself, such as immune globulin, neutrophils, and cytokines. Thus, these established methods are inflammation specific but do not adequately distinguish between infectious and noninfectious inflammation.[1,3]

Infection-specific imaging is performed with a variety of radiotracers that all label one of the consecutive steps of the host response to the invading organisms. Acute inflammation is characterized by hyperemia, increased endothelial permeability, exudation of proteins, and cellular migration predominantly involving granulocytes, whereas, in chronic infection, hyperemia and increased endothelial permeability are less prominent and infiltration with macrophages and lymphocytes is predominant. The choice of the optimal radiotracer therefore depends on the grade of inflammation, age of infection, availability, cost, and radiation exposure.[4]

The accumulation of these agents in inflamed tissue is based on different mechanisms. The first mechanism is uptake into inflamed tissue as a result of increased metabolism, either of inflammatory cells ([^{18}F]FDG, as a glucose analogue reflecting the energy demand of inflammatory cells) or of tissue-specific cells with increased activity as a reaction to inflammation (^{99m}Tc-MDP), reflecting the activity of osteoblasts as the active response of bone to inflammation. The second mechanism is nonspecific accumulation in the site of inflammation as a result of increased blood flow and enhanced vascular permeability (albumin, IgG). In the case of labeled activated leukocytes, the uptake mechanism involves intact chemotaxis and specific migration to the site of inflammation. ^{67}Ga-citrate binds to transferrin, with the complex undergoing extravasation at sites of inflammation because of increased blood flow and increased vascular permeability. ^{67}Ga-citrate also binds to lactoferrin, which is present in high concentrations in inflammatory foci. Most radiolabeled agents accumulate at sites of infection if the local blood flow and the vascular permeability are increased, but diphosphonates are unique in that several different mechanisms play a role in the accumulation of these