

^{18}F -FDG PET in Rheumatoid Arthritis: There Still Is a Long Way to Go

Rheumatoid arthritis (RA) is a chronic progressive disease with a high worldwide prevalence—860/100,000—and the highest incidence of all autoimmune diseases—21.8/100,000 in persons older than 16 y (1). RA is a multisystem disorder characterized by destructive synovitis and inflammation, both local and systemic. On the basis of this simple description, PET with ^{18}F -FDG as a metabolic tracer seems to be ideal for imaging RA. ^{18}F -FDG has long been known to be taken up by various cells in inflammatory lesions (2–5), and the possibility of whole-body imaging makes PET a promising candidate for detection and monitoring of infection and inflammation (6,7), as indicated by more than 100 articles on this topic found by a literature search using PubMed, the online service of the U.S. National Library of Medicine. However, a PubMed literature search on RA and ^{18}F -FDG PET retrieved only 7 articles, 6 of which were categorized as case reports. The only full study among these articles was published in 1995 by Palmer et al. (8). The authors performed ^{18}F -FDG PET and contrast-enhanced MRI of the wrist joint on 12 patients with inflammatory arthritis, 9 of whom had RA as defined by the criteria of the American Rheumatism Association (ARA) (9). Images were acquired after 2 wk of no treatment, after 2 wk of treatment with steroidal or nonsteroidal antiinflammatory drugs, and 12–14 wk after treatment with

methotrexate. ^{18}F -FDG uptake and the pannus volume estimated by MRI correlated strongly, as did changes in pannus volume and ^{18}F -FDG uptake after therapy. Furthermore, both parameters correlated strongly with clinical measures such as pain, tenderness, and swelling, although no correlation between PET or MRI of the wrist joint and overall clinical outcome was observed. On the basis of their data, the authors concluded that contrast-enhanced MRI and PET allow quantification of volumetric and metabolic changes in joint inflammation and comparison of the efficacies of antiinflammatory drugs (8).

Nine years later, another full paper on ^{18}F -FDG PET imaging of RA is presented by Beckers et al. (10), on pages 956–964 of this issue of *The Journal of Nuclear Medicine*. Twenty-one patients with RA according to the ARA criteria (9), as well as 3 healthy subjects and 10 melanoma patients referred for staging, underwent ^{18}F -FDG PET imaging. In all subjects, images of the knees and the joints of either the upper or the lower extremities were analyzed visually and quantitatively by measurement of the maximum standardized uptake value (SUV) of the respective joints. These data correlated with multiple clinical, biologic, and ultrasound findings. While metabolic activity was increased in the affected joints of patients with RA, ^{18}F -FDG PET findings were negative in all the joints of non-RA subjects. A significant linear correlation between SUV and the synovial thickness measured by ultrasound was found for all RA joints investigated except the metatarsophalangeal joints. The cumulative SUV of all PET-positive joints, as well as the number of positive joints in a patient, correlated significantly with

clinical parameters such as the number of tender and swollen joints, patient's and physician's global assessment scores, biologic measures such as erythrocyte sedimentation rate and C-reactive protein, ultrasound findings such as number of ultrasound-positive and Doppler-positive joints, and composite indices such as 28-joint counts and the simplified disease activity index (10). Both the number of PET-positive joints and the cumulative SUV increased with the number of positive clinical parameters (swelling, tenderness, and positive ultrasound findings). These extensive data led Beckers et al. to conclude that ^{18}F -FDG PET can assess the metabolic activity of synovitis and measure disease activity in RA by means of the number of PET-positive joints and cumulative SUV and that PET in general is a suitable and quantitative method for clinically evaluating RA patients (10).

Although this new approach to ^{18}F -FDG PET imaging of patients with RA is promising, the question arises whether PET, a rather expensive modality with still-limited accessibility, will become a future diagnostic tool in RA or will remain restricted to research. A pivotal point will be whether ^{18}F -FDG PET can show clinical benefit and cost-effectiveness by providing information critical to patient management. The fact that ^{18}F -FDG PET can detect synovitis and that the number of ^{18}F -FDG-positive joints correlates with other clinical parameters such as number of swollen or tender joints will not make ^{18}F -FDG PET a standard tool in the diagnostic workup of RA. The possibility of assessing disease activity (10) and metabolic changes in response to treatment (8), however, may turn ^{18}F -FDG PET into a useful diagnostic tool. Data provided by ^{18}F -FDG

Received Feb. 9, 2004; revision accepted Mar. 2, 2004.

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PET offer unique quantitative information on glucose metabolism that cannot be supplied by other imaging techniques. RA-induced changes of synovial tissue, cartilage, bone, and pararticular soft-tissue components, as well as effusion, are well described and can be detected by planar or tomographic radiography, bone scintigraphy, MRI, and ultrasound (11,12). More functional information and direct evaluation of synovitis, pannus formation, and erosions, the main characteristics of RA, can be obtained by ultrasound and Doppler ultrasound (13,14) or by contrast-enhanced, fat-suppressed MRI (8,15). As outlined by Beckers et al. (10), these techniques are sensitive in depicting the pannus and synovitis in an early stage of disease, allowing measurement of the thickness or volume of the inflamed synovia and enabling assessment of hypervascularization. But they are limited to morphology-based functional information and do not provide metabolic information. Furthermore, high-resolution, contrast-enhanced MRI is limited to imaging circumscribed areas of the body, such as one hand per procedure, whereas ultrasound is more observer dependent.

Unique metabolic information might be the basis for a potential role of ^{18}F -FDG PET in RA, and the findings of Palmer et al. (8) and Beckers et al. (10) encourage speculation on potential indications for diagnosis, assessment of disease activity, and monitoring response to therapy. According to the ARA, the diagnosis of RA is based on a combination of characteristic criteria obtained by medical history, physical examination, laboratory tests for serum rheumatoid factor, and conventional radiography, which is still considered the standard of reference for detecting joint involvement in RA (9). However, newer and more expensive therapeutic options demand early and reliable diagnosis, as they have been shown to stop both clinical and radiographic progression in early RA (16–18). The early stage of disease often presents clinically as single-joint involvement with predominantly soft-

tissue inflammation, such as synovitis and tenosynovitis, which may precede clinical symptoms and bony destruction. The disease can also present atypically, involving only a few scattered joints. Contrast-enhanced MRI and high-resolution ultrasound were more sensitive than radiography in detecting early joint involvement in RA (15), whereas conventional bone scanning is a sensitive whole-body method for screening joint inflammation (12,15). ^{18}F -FDG PET as a metabolic imaging device might be able to detect early signs of inflammation as reliably as can bone scanning and MRI, but only PET allows quantification of ^{18}F -FDG uptake, by which disease activity can be assessed and multiple joint areas followed up with reasonable effort.

Another interesting aspect of baseline ^{18}F -FDG PET before therapy is the potentially prognostic value of SUV. In oncology, pretherapeutic SUV has been shown to predict both the outcome of chemotherapy and disease-free and overall survival for many tumor entities. The underlying hypothesis is that more aggressive tumors are metabolically more active and, thus, show higher ^{18}F -FDG uptake. A similar hypothesis might work in RA as well: Beckers et al. (10) showed that SUV was significantly increased in joints with a positive Doppler signal, that is, in joints with neo- or hypervascularization, a characteristic of aggressive synovitis in RA. The cumulative SUV of all joints involved might be even more predictive than are the SUV values of single joints. The potential prognostic information of ^{18}F -FDG PET could be of enormous value for improving individual risk assessment, because the course of disease and the eventual outcome in RA is highly variable and hard to predict. As outlined by Landewe and van der Heijde (18), the heterogeneity of RA calls for an appropriate prediction of outcome at the individual-patient level so that an RA therapy regimen can be tailored to the specific needs of the patient.

Another future field for ^{18}F -FDG PET imaging of RA might be therapy monitoring. A variety of new drugs

and treatment modalities, including biologic and immunosuppressive agents, appear highly effective but have high costs and can have severe side effects (16–18). A quantitative instrument to monitor therapeutic effects and to predict whether a change in therapy will reduce side effects and minimize costs while still optimizing disease control would improve an individualized therapy approach (18). Palmer et al. (8) showed that quantitative ^{18}F -FDG PET helped to detect metabolic changes as measures of response to therapy that were not apparent with conventional clinical indexes or radiography. The authors therefore concluded that this technique is promising for monitoring and comparing the efficacy of antiinflammatory drugs and that an objective treatment response would likely be attained after a shorter course of therapy than with conventional clinical and radiographic parameters (8). Thus, ^{18}F -FDG PET might be a useful tool to monitor therapy-induced changes in joint inflammation and to predict the outcome after an early onset of treatment.

In conclusion, the results presented by Beckers et al. (10) and the earlier work by Palmer et al. (8) are a promising starting point for further prospective studies on ^{18}F -FDG PET imaging of patients with RA. However, much work remains to be done to gain more detailed information and to clarify the impact of ^{18}F -FDG PET on diagnosis and therapy of RA, in comparison with state-of-the-art MRI, ultrasound, and three-phase bone scanning. Eventually, we may be able to define indications for ^{18}F -FDG PET to improve and adjust RA management.

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