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Increased FDG uptake suggests synovial inflammatory reaction with osteoarthritis: preliminary in vivo results in humans

MA. Parsons¹, M. Moghbel², B. Saboury¹, DA. Torigian¹, TJ. Werner¹, D. Rubello³, S. Basu⁴, and A. Alavi¹

¹Department of Radiology, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania

²Stanford University School of Medicine, Stanford, California

³Department of Nuclear Medicine, PET/CT Centre, Radiology, NeuroRadiology, Medical Physics, 'Santa Maria della Misericordia' Hospital, Rovigo, Italy

⁴Radiation Medicine Centre (B.A.R.C), Tata Memorial Centre Annexe, Jerbai Wadia Road, Parel, Mumbai 400012, India

Abstract

The objective of this prospective study was to compare the metabolic activity of the knee joints of a group of subjects with painful knees clinically (as recurrent joint pain, joint instability and functional limitations) consistent with osteoarthritis (OA) and those of another group of patients without such complaints, using FDG-PET imaging. A total of 97 subjects who participated in either painful joint prosthesis or diabetic foot research studies involving FDG-PET scans were asked to complete a knee pain questionnaire. The patients were asked whether they experienced pain in any joint, and if so, which joints were affected. A total of 18 knee joints without prosthesis were reported to be painful. The maximum SUVs (SUV_{max}) of the middle joint space and lateral synovial tissue of these 18 knees were measured and compared to those of a set of subjects with control asymptomatic knees. The average SUV_{max} of the middle part of the joint space in the painful knees was 1.35 ± 0.59 , as compared to an average SUV_{max} value of 0.86 ± 0.14 in the control group ($p = 0.0176$). The average SUV_{max} of the synovium in the lateral part of the painful joints was 1.17 ± 0.49 , as compared to 0.73 ± 0.31 in the control group ($p = 0.0161$). These data indicate that increased FDG uptake is associated with knee pain in OA patients, and that there is a positive relationship between the two parameters.

Keywords

Osteoarthritis; FDG uptake; Synovial tissue; Pathophysiology

Address Correspondence to: Abass Alavi, Division of Nuclear Medicine, Department of Radiology, Hospital of the University of Pennsylvania, 3400 Spruce Street, Philadelphia, PA 19104; Phone: 215-662-3069; Fax: 215-573-4107. abass.alavi@uphs.upenn.edu.

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Introduction

Osteoarthritis (OA) is the most common arthritic condition worldwide in humans, although its prevalence varies according to the diagnostic criteria used and the specific joint(s) under study [1]. The hip and knee are the most commonly affected large joints; joint disease of the knee affects approximately 8% of the population at any given time [2], and as many as 40% of people aged over 65 may have symptomatic OA of the knee or hip [3]. In addition to the degradation process, inflammation plays a fundamental role in the development of OA [4–6]. Clinical symptoms include recurrent pain in one or more joints, joint instability, and functional limitations of both an occupational and recreational nature. As the disease progresses, symptoms progress in severity and become increasingly debilitating for the patient. Unfortunately, much of the damage has already taken place by the time of clinical presentation, and so management is aimed at symptomatic relief rather than reversal of the disease process.

Currently, the diagnosis of OA is based on clinical findings of symptoms such as knee pain, short-lived morning stiffness, and functional limitations, as well as physical signs such as crepitus, restricted movement, and bony enlargements providing strong evidence of disease. Plain film radiography is often used to corroborate a clinical diagnosis [7]. However, it is frequently months to years into the disease process before a diagnosis is made on these grounds. Prior studies of [18F]-2-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) have shown promise for the use of FDG activity as an indication of early inflammatory changes in rheumatoid arthritis (RA) and associated synovitis [8–11]. The objective of this study was to investigate the potential application of FDG-PET in osteoarthritis by comparing the FDG activity of the knees in subjects with painful knees to that in normal controls.

Materials and Methods

Patient data included in this analysis were drawn from two other prospective studies: one study on the application of FDG-PET in painful joint prosthesis and infection [12] and another on the application of FDG-PET in diabetic foot [13]. Both studies were performed at the Hospital of the University of Pennsylvania with Institutional review board (IRB) approval. Patient inclusion and exclusion criteria and FDG-PET imaging were described in earlier publications [12, 13]. As a part of these studies, lower extremity PET scans were performed approximately 60 minutes after the intravenous injection of 140 $\mu\text{Ci/kg}$ (5.2 MBq/kg) of ^{18}F -FDG. Prior to the injection of ^{18}F -FDG, all patients fasted for at least 6 hours and had blood sugar levels of ≤ 200 mg/dl.

From these two studies, patients with osteoarthritic symptoms of the knee and with FDG-PET imaging of the knees were included in our analysis. For this purpose, we administered an osteoarthritis questionnaire to all patients enrolled in the painful joint prosthesis and diabetic foot studies. A total of 97 patients were asked to complete the OA questionnaire, which consisted of 11 questions related to the patient's history of joint pain and arthritis. The question of particular importance in this retrospective analysis was, "Do you have, or have you ever had, pain in a joint? If yes, what joint?" The questionnaire administered to

these patient populations was based on the assumption that these patients may have a high likelihood of OA given their prior joint disease (i.e., need for arthroplasty) and average age.

The FDG-PET images of both groups of subjects enrolled in this study were analyzed quantitatively. For each knee that was examined, SUV_{max} was measured using two-dimensional regions of interest in two areas of interest: one in the central region of the joint space (based on degree of uptake) on the axial images, and another in the most active site (either the medial or lateral synovial tissue) on axial or coronal images. For a control group, patients with no symptoms of joint pain or history of joint prosthesis in the corresponding joint were selected, and the FDG-PET images of their knees were analyzed in an identical manner to that of the OA group. To ensure that our data represented the pathological conditions related to OA, knees with prosthesis, or other accompanying lesions, were excluded from our study.

Statistical analysis was performed using an unpaired two-tailed *t*-test assuming equal variances. The GraphPad Prism® 4 (GraphPad Software, Inc. San Diego, CA) was used for statistical analyses. $P < 0.05$ were considered as statistically significant.

Results

Among the 97 subjects who received the questionnaire, 13 patients (with 18 painful knees) were identified to meet the criteria for OA (six with right knee pain, two with left knee pain, five with bilateral knee pain). None had a prosthetic implant in the painful joint. Of them, 9 patients were drawn selected from the painful joint prosthesis study and four were from the diabetic foot study. Five had a prosthesis placed in the contralateral knee while seven had an ipsilateral hip prosthesis. Six were female, seven were male, and the average age was 62.3 years (Table 1).

FDG uptake in the painful knees was significantly higher than in the controls. This increase in uptake was noted in middle joint space in 77.7% of cases and in the synovium in 83.3% of cases. The SUV_{max} measured in the painful knees also consistently exceeded that measured in control knees. The average SUV_{max} of the center region of the joint space in the painful knees was 1.35 ± 0.59 (95% confidence interval (95% CI: 1.05 to 1.65)), as compared to 0.86 ± 0.14 (95% CI: 0.76 to 0.96) in the control group ($p = 0.0176$).

Furthermore, the average SUV_{max} of the synovium in the lateral part of the painful joints was 1.17 ± 0.49 (95% CI: 0.93 to 1.42), as compared to 0.73 ± 0.31 (95% CI: 0.51 to 0.95) in the control group ($p = 0.0161$) (Figure 1). Representative examples of these FDG-PET scans are also shown in Figure 2.

Discussion

Osteoarthritis is characterized by a progressive loss of articular cartilage, new bone formation and remodeling, and synovial proliferation and inflammation [4, 14]. Patients with OA typically present with complaints of progressive joint pain and stiffness that has been ongoing for months to years. In the past, clinical assessment by an experienced physician has been the reference standard in diagnosing and treating patients with OA. However, clinical assessment is generally unable to detect the disease at its early stages, and

therefore disease-modifying maneuvers and interventions have not been employed in a timely manner. PET imaging with FDG as a surrogate marker for glucose utilization allows for the measurement of cellular metabolism in normal and pathological states. Increased FDG uptake in painful joints represents ongoing tissue inflammation, as has been demonstrated in studies of similar disease states [15, 16].

Although it is well known that FDG uptake correlates with inflammatory joint disease [17–19] and other inflammatory etiologies [20, 21], few studies are available about the potential usefulness of FDG-PET as an imaging tool in the early diagnosis of OA. An analysis of FDG-PET imaging for degenerative spinal disease in 150 patients revealed that it was a common incidental finding (in 22% of patients) on PET, most commonly seen in the lumbosacral spine, and that the severity of FDG-PET findings correlated with the severity of degenerative disc and facet disease as graded by CT [18]. Evaluation of FDG-PET imaging in 15 patients with medial-type knee OA and correlation with magnetic resonance imaging (MRI) findings revealed that FDG uptake of the whole knee was higher in OA than in controls. Moreover, the authors reported that FDG generally accumulated in periarticular lesions, with higher activity in the medial condylar region than in the lateral condylar region in OA, and that periosteophytic accumulation was found in half of cases with osteophytes [10]. It was also shown that diffuse FDG uptake is associated with signs and symptoms of OA or bursitis [8].

A few other studies have explored the value of FDG-PET imaging in the assessment of RA. As both OA and RA are characterized by chronic inflammation, it would be helpful to compare FDG-PET findings in the RA cases with those in the OA cases. In RA patients, Beckers et al. found FDG-PET positivity in 69% of joints and reported that FDG uptake was correlated with MRI and ultrasound assessments in patients with RA [9, 22]. The number of PET-positive joints and the cumulative SUV were significantly correlated with other symptoms and signs of arthritis, including swelling and tenderness of the joints, synovial thickness, patient and physician assessments, erythrocyte sedimentation rate, and C-reactive protein serum levels [9, 22]. Research by Kubota et al in multiple large joints in patients with RA revealed that FDG uptake correlated with the degree of arthritic inflammation and that FDG uptake was also significantly different in patients in remission compared to patients with active arthritis [23]. In addition, it was reported that FDG uptake in patients with active RA was significantly correlated with disease severity and may be predictive of response to therapy with the anti-tumor necrosis factor alpha antibodies such as infliximab [24] and prognostic of clinical outcome [25].

Findings in other types of arthritis also suggest a valuable role of FDG-PET imaging in clinical diagnosis, including psoriatic arthritis [26, 27], collagen vascular diseases-(CVD)-associated arthritis [28], juvenile idiopathic arthritis [29], ankylosing spondylitis [30], and reactive arthritis [31]. However, the data that are available on this topic are still quite limited; further studies are needed with serial assessments of patients to establish if levels of FDG uptake in osteoarthritic joints correlate with disease severity as the disease progresses or regresses, or if they correlate with responses to therapy and long-term prognoses. If validated, FDG-PET may serve as a valuable non-invasive imaging modality not only for the diagnosis of early arthritis but also for early response monitoring to therapeutic

interventions and for prevention of OA complications such as debilitating pain and need for joint replacement.

In this study, we demonstrated that FDG uptake in the painful knees was significantly higher than that of the control group, both in the medial compartment and surrounding synovial tissues. Our findings indicate that FDG-PET imaging, as a non-invasive quantitative method, correlates with patients' symptoms of knee pain and has the potential to quantitatively evaluate knee inflammation in OA. As such, FDG-avid inflammatory process may serve as an early biomarker for the presence and severity of disease, allowing for treatment to be initiated or modified appropriately.

The limitations of this study include the number of subjects investigated and the lack of correlation with pathological findings. Furthermore, the lack of correlation of FDG uptake with disease stage and severity, as well as the lack of clinical follow-up data for correlating FDG uptake with disease progression or response to therapy, limits our ability to elucidate the diagnostic value of FDG-PET in guiding therapy selection and predicting outcomes in patients with this debilitating disease. Finally, the volume of inflammatory changes was not considered in this study, which may prove to be a clinically useful measure.

In summary, our data indicate that increased FDG uptake as measured by PET imaging is associated with pain in joints thought to be affected by OA. Thus, FDG-PET imaging may hold an application as a non-invasive diagnostic tool to detect knee joint inflammation and to assess disease severity in the clinical setting.

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Figure 1. Semi-quantitative measurement of FDG uptake in the painful knees versus control knees. A. SUV_{max} in the middle joint space. B. SUV_{max} in the surrounding synovium. The error bars indicate SE values in each group.

Figure 2.

FDG-PET images of the knees reveal low FDG uptake in control knees but increased uptake in the painful knees. A and B: FDG uptake in a typical control knee (with no pain). C and D: FDG uptake in a painful knee (this patient had bilateral chronic knee pain and left side prosthesis placement). Both axial (A and C) and coronal (B and D) images of knees are shown. SUV_{max} data for the control knee in A and B were as follows: Right central joint space = 0.8; right synovium = 0.4; left central joint space = 0.9; left synovium = 0.5. For the painful knee in C and D, SUV_{max} were 1.3 and 1.4, respectively, for the right central joint space and the right surrounding synovial tissues. There was even higher FDG uptake (SUV_{max} 2.0) in the left knee associated with a prosthesis placement that was not included in the analysis.

Table 1

Patient characteristics

Patient (n=13)	
Sex	7 male; 6 female
Age (years)	62.3 (44–81) mean (range)
Cases from painful prosthesis study	5 with hip prosthesis; 4 with knee prosthesis
Cases from diabetic foot study	4 with diabetic foot pathology
Joint (n=18)	
Sidedness	11 Right knees; 7 Left knees
Relationship to prosthesis	5 contralateral to painful knee prosthesis; 7 ipsilateral to painful hip prosthesis