

RESEARCH ARTICLE

2-Deoxy-2-[F-18]fluoro-D-glucose Joint Uptake on Positron Emission Tomography Images: Rheumatoid Arthritis Versus Osteoarthritis

E. H. Elzinga,¹ C. J. van der Laken,¹ E. F. I. Comans,² A. A. Lammertsma,²
B. A. C. Dijkmans,¹ A. E. Voskuyl¹

¹Department of Rheumatology, VU University Medical Centre, Amsterdam, The Netherlands

²Department of Nuclear Medicine and PET Research, VU University Medical Centre, Amsterdam, The Netherlands

Abstract

Purpose: Previous positron emission tomography (PET) studies have shown increased 2-deoxy-2-[18F]fluoro-D-glucose (FDG) uptake in joints of patients with osteoarthritis (OA) and inflamed joints of patients with rheumatoid arthritis (RA). This study compares FDG uptake in joints of RA and OA patients and FDG-uptake with clinical signs of inflammation.

Procedures: FDG-PET scans of hands and wrists were performed in patients with RA and primary OA. PET data were compared with clinical data.

Results: 29% of RA joints and 6% of OA joints showed elevated FDG-uptake. The level of uptake in PET-positive OA joints was not significantly different from that in RA joints. The majority of PET results of RA joints corresponded with clinical findings. Clinical synovitis was found some OA joints with FDG-uptake.

Conclusions: FDG-uptake was observed in the majority of clinically inflamed RA joints and in a few OA joints with no significant difference in uptake level. The latter may be due to secondary synovitis.

Key words: FDG, Rheumatology, Rheumatoid arthritis, Osteoarthritis

Introduction

In clinical practice, 2-deoxy-2-[F-18]fluoro-D-glucose (FDG) uptake is often observed in large joints on whole body images, most likely due to degenerative changes and aging [1–3]. In fact, diffuse FDG shoulder uptake on positron emission tomography (PET) was associated with clinical findings of osteoarthritis (OA) [1], and FDG uptake in the vertebral column was caused by degenerative changes in facet joints [2]. FDG joint uptake may also reflect arthritis because FDG uptake has also been noticed in inflamed joints of autoimmune diseases, among which is

rheumatoid arthritis (RA) [4–6]. RA is a chronic inflammatory disease in which small hand and feet joints are predominantly affected, but large joints may also be involved. Due to technical limitations, among which is attenuation, FDG uptake in small hand joints is usually not seen on whole-body images. To date, a direct comparison between FDG uptake in inflamed joints of patients with RA and degenerative joints of patients with OA has not been made. It is unclear whether the level of FDG uptake in inflamed joints of RA patients differs from that of degenerative joints.

The aims of the present study were (1) to compare FDG uptake in hand and wrist joints of patients with RA and OA and (2) to assess whether there is a relation between FDG uptake and clinical findings.

Correspondence to: E. H. Elzinga; e-mail: eh.elzinga@vumc.nl

Materials and Methods

Patients

A total of 25 patients were included, of which 14 (10 women, 4 men) had been diagnosed with RA, 6 (all women) with primary OA, and 5 (all women) with fibromyalgia (FM). FM patients were included as a control group because FM is a syndrome with no known anatomical abnormalities and/or inflammatory symptoms. The mean ages of RA, OA, and FM patients were 57 ± 7 , 55 ± 11 , and 32 ± 11 years, respectively. RA patients fulfilled American College of Rheumatology criteria [7] for their diagnosis and had active RA with a mean disease activity score (DAS28) of 5.2 ± 0.7 . The mean disease duration of RA patients was 9 ± 6 years (range 1–22 years). All included RA patients were on treatment with one or two disease-modifying drugs (methotrexate $n=12$, sulfasalazine $n=2$, hydroxychloroquine $n=1$, and leflunomide $n=1$). In addition, seven RA patients were treated with nonsteroidal anti-inflammatory drugs and three patients were treated with prednisone with at a maximum dose of 10 mg daily. This study focuses on inflammation in hand and wrist joints because of the predominant localization of RA in small joints. Only patients with arthritis of at least two hand or wrist joints were included. At inclusion, a rheumatologist determined disease activity in hand joints and wrists. Large joints were not included in this study. In RA patients, all metacarpophalangeal (MCP), proximal interphalangeal (PIP), and wrist joints were evaluated (total number of 22 joints per patient). At the time of scanning, at least two clinically swollen joints of hands and/or wrists were present. In addition to evaluation of MCP, PIP, and wrist joints, in OA patients, the carpometacarpal 1 (CMC1) and all distal interphalangeal (DIP) joints were also evaluated, as these joints are frequently affected in primary OA but not in RA (total of 32 joints per OA patient). All OA patients had at least one clinically affected joint at inclusion. In both RA and OA patients, all hand and wrist joints were scored for clinical synovial swelling. Hand and wrist joints of FM patients lacked clinical signs of OA and synovial swelling, which was determined by clinical examination of MCP, PIP, DIP, CMC1, and wrist joints. The study protocol was approved by the medical ethics committee of the VU University Medical Centre. All patients gave written informed consent prior to scanning.

PET Imaging Acquisitions

PET scans were performed using a ECAT EXACT HR+ scanner (CTI/Siemens, Knoxville, TN, USA). This whole-body scanner enables the acquisition of 63 contiguous transaxial slices, covering an axial field of view of 15.5 cm. Prior to scanning, patients fasted for at least 6 h. Plasma glucose levels, measured just prior to intravenous administration of FDG, were all within normal limits. Patients with a bodyweight of less than 85 kg were injected with 370 MBq [^{18}F]FDG, otherwise injected dose was increased to 555 MBq. After a resting period of 60 min, to allow for uptake of FDG,

patients were transferred to the scanning room. Whole-body images were not suitable for investigation of the hand and wrist joints because FDG uptake in small hand joints is not seen on whole-body images with the arms of the patients positioned adjacent to the body. The latter is caused by attenuation in and scattered radiation from the pelvic region, the proximity of the bladder, and the limited spatial resolution at the edge of the transaxial field of view. Therefore, a static emission scan of 5 min of hands and wrists was acquired, following positioning of hands and wrists in the center of the field of view of the scanner. 2-D data acquisition was used. PET scans were corrected for decay, scatter, attenuation, randoms, and dead time. Images were reconstructed as 128×128 matrices using filtered back projection with a Hanning filter (cut-off 0.5 cycles/pixel), resulting in a transaxial spatial resolution of ~ 7 mm full width at half maximum.

Image Analysis

Coronal, sagittal, and transverse images were used for analysis. All hand and wrists joints, as mentioned above, were investigated. First, uptake in joints was scored as positive in case of focally increased uptake of FDG. Next, regions of interest (ROIs) were drawn on PET-positive areas in these joints. Control regions were drawn on metacarpal bone outside these joints. Joint-to-control (J/C) ratios were calculated, giving semiquantitative data. In joints without focally increased FDG uptake, no further analysis was performed. Control ROIs were drawn upon MCP joints of FM patients to allow comparison of J/C ratios with RA and OA. Finally, PET data were compared with clinical data.

Statistical Analysis

Differences of the mean J/C ratios between RA, OA, and FM joints were compared using multilevel analysis because the observations of joints within one patient are highly correlated. Multilevel analysis [8] is a regression technique that takes into account possible dependency of observations. In this situation, two levels are considered: joints within patients. An independent-samples *t* test was used to compare the number of PET-positive joints between RA, OA, and FM.

Results

Clinical Data

Of the 22 hand and wrists joints evaluated, the mean number of clinically swollen joints per RA patient was seven (range 2–17). In OA patients, the number of joints (out of 32 evaluated joints) with (secondary) synovial

Table 1. Comparison of the percentage of joints with and without FDG uptake in RA, OA and FM patients, together with the level of uptake in positive joints, expressed as J/C ratios

Group	Total number of investigated joints	Total number of joints with clinical synovial swelling	PET positive joints	PET negative joints	J/C ratio of joint uptake on PET (mean \pm SD)
RA	308	94 (31%)	88 (29%)	220 (71%)	5.4 (± 1.2)
OA	192	3 (2%)	12 (6%)	128 (97%)	3.7 (± 1.7)
FM	110	0	0 (0%)	110 (100%)	1.7 (± 0.5)

In addition, the number of joints with clinical synovial swelling is included

swelling ranged from 0 to 2. No signs of synovial swelling were observed in joints of FM patients. The total number of joints with clinical swelling in the RA, OA, and FM groups is listed in Table 1.

FDG Images

In Fig. 1, FDG uptake images are shown of hands and wrists of representative patients from each patient group. The number of PET-positive joints in RA patients was significantly higher than in OA patients ($p < 0.001$) (Table 1). No FDG uptake was found in joints of FM patients. FDG uptake was noticed in only 12 out of 192 OA joints investigated. The level of FDG uptake in these joints did not differ significantly

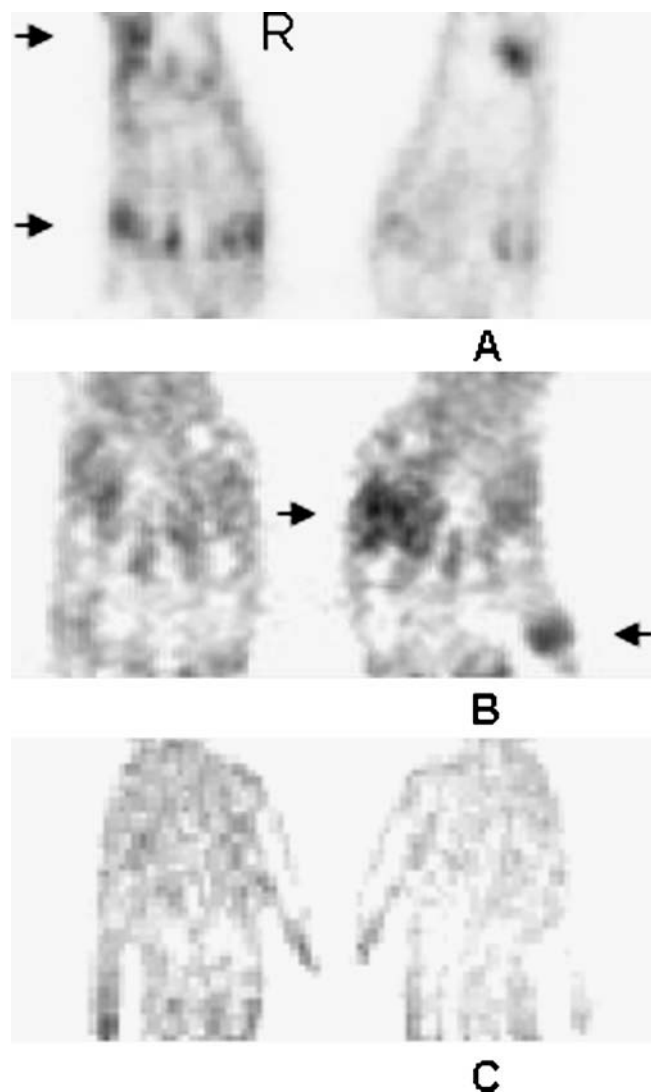


Fig. 1. PET images of **A** an RA patient with FDG uptake in MCP joints and both wrists (arrows); **B** an OA patient with FDG uptake in CMC1, the base of the second metacarpal joint, and PIP 5 (arrows); and **C** an FM patient without FDG uptake

from that in RA joints. FDG uptake in joints of RA and OA patients was significantly higher than that in FM patients ($p = 0.01$ and $p = 0.03$, respectively). Background activity in synovial tissue was slightly higher than in metacarpal bone, hence the elevated J/C ratio in FM patients (Table 1).

Relation between FDG Images and Clinical Data

RA Patients In 76% of the joints, there was correspondence between clinical findings and PET results, i.e., the majority of joints with synovial swelling showed increased FDG uptake and, vice versa, most joints without clinical signs of inflammation showed normal FDG uptake. Nevertheless, discrepancies between FDG images and clinical examinations were noticed. In 13% (41 out of 308) of RA joints, there were signs of clinical synovitis, whereas no focally increased FDG uptake was seen. In addition, 11% (35 out of 308) of RA joints evaluated did not show any clinical signs of inflammation while locally enhanced FDG uptake was observed.

OA and FM Patients Twelve of the joints evaluated in OA patients (6%) showed increased FDG uptake. Three of these joints showed synovial swelling (secondary to OA) at clinical evaluation. No FDG uptake was observed in any of the joints of FM patients, in agreement with the absence of synovial swelling in all these joints.

Discussion

In the present study, most RA joints with clinical signs of inflammation showed increased FDG uptake. The number of PET-positive joints in RA patients was significantly higher than that in OA patients. The level of FDG uptake was, however, similar in PET-positive RA and OA joints. The control joints of FM patients, without clinical signs of inflammation and degenerative changes, did not show any uptake.

A small number of OA joints showed FDG uptake. Unfortunately, x-rays of the hands of these OA patients were not available. Therefore, it was not possible to correlate FDG uptake with signs of OA. FDG uptake in OA joints could be due to several factors. First, increased FDG uptake may reflect enhanced metabolic activity in bone/cartilage due to an inflammatory process involved in the mechanism of cartilage destruction [9]. Alternatively, secondary synovitis in osteoarthritic joints may also result in increased FDG uptake in OA joints, as has been studied by ultrasound [10]. This second possibility is supported by the present observation that three out of 12 OA joints with FDG uptake showed synovial swelling at clinical examination.

Although patients had active disease at inclusion, the actual number of PET-positive joints in RA patients was relatively low (29%). This can be explained by the fact that

only 31% of the investigated hand joints of RA patients showed synovial swelling at the time of scanning. The FDG PET results corresponded in the majority (76%) of evaluated joints with clinical assessment of synovial swelling. This finding corresponded to observations in RA patients by Beckers et al. [5], who compared FDG PET with ultrasound and clinical examination of joints. In addition, Goerres et al. [11], showed matched clinical and FDG-PET results in 78% of joints of RA patients responding to infliximab therapy.

Although these two former studies have also compared FDG-PET to clinical findings in RA patients, no comparison has been made between FDG-PET in RA patients and OA patients, which was the focus of our study. In addition, previous FDG studies in RA patients did not include a control group without inflammatory joint disease.

Despite matching of PET and clinical data in most of the joints investigated, absence of a PET signal was found in 13% of RA joints with clinical synovial swelling. Clinically inflamed joints may lack increased FDG uptake as a result of severe deformations of the joints, which may also have hampered the judgement of the presence of clinical synovitis. The latter explanation is strengthened by the fact that the observed mismatch between clinical signs of inflammation and lack of increased FDG uptake could be reduced by a factor of two if patients with severe joint deformation were excluded from the analysis. It should be noted that clinical judgement of synovitis can also be difficult in case of fibrotic synovial tissue, which may mimic synovitis [12]. Furthermore, additional mismatching of FDG PET and clinical data was found in 11% of the evaluated joints, in which FDG uptake was observed in the absence of clinical signs of inflammation. A positive signal on FDG-PET in clinically noninflamed joints may indicate visualization of subclinical synovitis. Subclinical synovitis has been found in histological studies of synovial tissue by Kraan et al. [13]. Recently, another study, using ultrasound, has suggested frequent occurrence of subclinical synovitis [14]. Apart from subclinical inflammation, secondary OA in RA may have caused enhanced joint uptake, as mentioned earlier.

The FM group appeared to be a useful control group with no FDG uptake in clinically noninflamed joints. The mean age of FM patients was, however, lower than that of RA and OA patients. This could actually be an advantage, as degenerative joints in elderly patients are more likely to show FDG uptake [3]. The joints of the induced FM patients did not show any clinical signs of OA.

In conclusion, FDG uptake is primarily seen in active (subclinical) inflamed RA joints. It may, however, also be

present in degenerative joints and in synovitis secondary to OA. Distinction between tracer uptake in RA and OA joints is not possible using FDG-PET. More specific evaluation of inflamed rheumatoid joints may become feasible by development of new PET tracers that specifically target molecular pathways associated with rheumatoid synovitis. As a potentially very sensitive method of imaging (pico- to nanomolar concentrations), PET may eventually become a useful tool in detecting synovitis at an early stage of RA, allowing early treatment.

Acknowledgements. Dr. GHC Schardijn, rheumatologist, is acknowledged for his contribution in to this study by referring patients with FM and patients with OA.

Ethics Approval. The study protocol was approved by the medical ethics committee of the VU University Medical Centre. All patients gave written informed consent prior to scanning.

References

1. Wandler E, Kramer EL, Sherman O, et al. (2005) Diffuse FDG shoulder uptake on PET is associated with clinical findings of osteoarthritis. *Am J Roentgenol* 185:797–803
2. Houseni M, Chamroonrat W, Zhuang H, et al. (2006) Facet joint arthropathy demonstrated on FDG-PET. *Clin Nucl Med* 31:418–419
3. Von Schulthess GK, Meier N, Stumpe KD (2001) Joint accumulations of FDG in whole body PET scans. *Nuclearmedizin* 40:193–197
4. Polisson RP, Schoenberg OI, Fischman A, et al. (1995) Use of magnetic resonance imaging and positron emission tomography in the assessment of synovial volume and glucose metabolism in patients with rheumatoid arthritis. *Arthritis Rheum* 38:819–825
5. Beckers C, Ribbens C, Andre B, et al. (2004) Assessment of disease activity in rheumatoid arthritis with [¹⁸F]-FDG PET. *J Nucl Med* 45:956–964
6. Blockmans D, De Ceuninck L, Van der Schueren S, et al. (2007) Repetitive 18-fluorodeoxyglucose positron emission tomography in isolated polymyalgia rheumatica: a prospective study in 35 patients. *Rheumatology* 46:672–677
7. Arnett FC, Edworthy SM, Bloch DA, et al. (1988) The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 31:315–324
8. Twisk JWR (2006) Applied multilevel analysis. Cambridge: Cambridge University Press, pp Twisk JWR (2006) Applied multilevel analysis. Cambridge: Cambridge University Press
9. Loesser RF (2006) Molecular mechanisms of cartilage destruction: mechanics, inflammatory mediators, and aging collide. *Arthritis Rheum* 54:1357–1360
10. D'Agostino MA, Conaghan P, Le Bras M, et al. (2005) Euler report on the use of ultrasonography in painful knee osteoarthritis part I: prevalence of inflammation in osteoarthritis. *Ann Rheum Dis* 64:1703–1709
11. Goerres GW, Forster A, Uebelhart D, et al. (2006) F-18 FDG whole body PET for the assessment of disease activity in patients with rheumatoid arthritis. *Clin Nucl Med* 31:386–390
12. Schmid M, Rodemann HP, Aicher WK (2004) Frequency of terminally differentiated fibroblasts in the synovial membrane of rheumatoid arthritis patients. *Z Rheumatol* 63:483–489
13. Kraan MC, Versendaal H, Jonker M, et al. (1998) Asymptomatic synovitis precedes clinically manifest arthritis. *Arthritis Rheum* 41:1481–1488
14. Wakefield RJ, Green MJ, Marzo-Ortega H, et al. (2004) Should oligoarthritis be reclassified? Ultrasound reveals a high prevalence of subclinical disease. *Ann Rheum Dis* 63:382–385