

Original article

**Prediction of Large Joint Destruction in Patients with Rheumatoid Arthritis Using
¹⁸F-FDG PET/CT and Disease Activity Score**

Short title: Large joint destruction of RA and FDG-PET/CT

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Abstract

Background

The assessments of joint damage in patients with rheumatoid arthritis (RA) are mainly restricted to small joints in the hands and feet. However, the development of arthritis in RA patients often involves the large joints, such as the shoulder, elbow, hip, knee and ankle. Few studies have been reported regarding the degree of large joint destruction in RA patients. ¹⁸F-fluorodeoxyglucose positron emission tomography combined with computed tomography (FDG-PET/CT) visualizes the disease activity in large joints affected by RA. In this study, the associations between destruction of the large joints and the findings of FDG-PET/CT as well as laboratory parameters were investigated, and factors associated with large joint destruction after the administration of biological therapy were identified in RA patients.

Methods

A total of 264 large joints in 23 RA patients (six males and 17 females; mean age of 66.9 ± 7.9 years) were assessed in this study. FDG-PET/CT was performed at baseline and six months after the initiation of biological therapy. The extent of FDG uptake in large joints (shoulder, elbow, wrist, hip, knee and ankle) was analyzed using the maximum standardized uptake value (SUV_{max}). Radiographs of the 12 large joints per patient obtained at baseline and after two years were assessed according to Larsen's method. A

logistic regression analysis was performed to determine the factors most significantly contributing to the progression of joint destruction within two years.

Results

Radiographic progression of joint destruction was detected in 33 joints. The SUVmax at baseline and six months and the disease activity score (DAS) 28 – erythrocyte sedimentation rate (ESR) at six, 12 and 24 months were significantly higher in the group with progressive joint destruction. The SUVmax at baseline and DAS28-ESR at six months were found to be factors associated with joint destruction at two years ($p < 0.05$).

Conclusion

The FDG uptake in the joints with destruction was higher than that observed in the joints without destruction. The SUV max at baseline and the DAS28–ESR at six months after the biological treatment were identified to be significant factors predicting destruction of the large joints at two years.

Abbreviations

ACPA : anti-cyclic citrullinated peptide antibody

ADA : adalimumab

CDAI : clinical disease activity index

CI : confidence interval

CRP : C-reactive protein

DAS28 : disease activity score in 28 joints

CT : computed tomography

DMARDs : disease-modifying antirheumatic drugs

ESR : erythrocyte sedimentation rate

ETN : etanercept

FDG : ¹⁸F-fluorodeoxyglucose

HAQ : Health Assessment Questionnaire

IFX : infliximab

MMP-3 : matrix, metalloproteinase-3

MRI : magnetic resonance imaging

MTX : methotrexate

OR : odds ratio

PDUS : power Doppler ultrasonography

PET : positron emission tomography

PSL : prednisolone

RA : rheumatoid arthritis

RF : rheumatoid factor

ROI : region of interest

SD : standard deviation

SDAI : simplified disease activity index

SUV : standardized uptake value

SUVmax : maximal standardized uptake value

TCZ : tocilizumab

TNF : tumor necrotic factor

US : ultrasonography

VAS : visual analog scale

Key words: Joint destruction, large joint, ^{18}F -FDG PET/CT, biological therapy, rheumatoid arthritis

Introduction

Rheumatoid arthritis (RA) is a systemic, inflammatory autoimmune disorder characterized by chronic inflammation of the joints and bone destruction. The recent development of biologics, such as tumor necrotic factor (TNF)-blocking agents, for the treatment of RA has improved the outcomes of the disease, and remission remains the ideal aim in patients with RA.¹ Obtaining a prompt and accurate diagnosis and providing early aggressive treatment using biologics are keys to achieving effective management in cases of RA.² Since increased joint damage may cause functional impairments, it is important to inhibit radiographic progression and predict consequent joint destruction.

Recent investigations have shown that power Doppler ultrasonography (PDUS) is useful for predicting joint destruction of the hands in RA patients.³⁻⁵ PDUS detects the synovial perfusion in the inflamed joints, and the synovial perfusion detected on PDUS is related to subsequent radiographic progression.⁴ Although these assessments of joint damage are mainly restricted to small joints in the hands and feet, the development of arthritis in RA patients often involves the large joints, such as the shoulder, elbow, hip, knee and ankle, in addition to the fingers.⁶ Since radiographic damage, the damage that is radiographically detectable, of large weight-bearing joints is strongly associated with a disability in walking and functions as an important determinant of the functional capacity in patients with RA,^{7,8} it is indispensable to assess the extent of radiographic damage in these joints. However, few previous reports have studied the predictive value of radiographic findings for destruction

of the large joints in RA patients.

¹⁸F-fluorodeoxyglucose (FDG) - positron emission tomography (PET) imaging may be employed to assess the metabolic activity of synovitis directly and measure the disease activity in large joints affected by RA.^{6, 9-11} Whole-body FDG-PET combined with computed tomography (CT) (FDG-PET/CT) is able to visualize the disease activity in large joints affected by RA.⁶ Furthermore, the response on FDG-PET correlates with the clinical response to biologic treatment in cases of RA.¹²⁻¹⁴ However, it is not thoroughly understood whether ¹⁸F-FDG PET/CT findings correlate with the severity of destruction in the large joints of the RA patients. The purpose of this study was therefore to investigate the associations between destruction of the large joints and ¹⁸F-FDG PET/CT findings, the disease activity and laboratory parameters in RA patients.

Materials and Methods

Subjects

The Institutional Review Board of our hospital approved the protocol for this study. Between May 2010 and November 2012, 23 patients (six males, 17 females; mean age, 66.9 ± 7.9 years) were enrolled. Based on the power analysis with G*Power 3 (Faul, Erdfelder, Lang& Buchner, 2007: <http://www.psych.uni-duesseldorf.de/abteilungen/aap/gpower3/>), the sample size of this

study was calculated enough to supply 80 percent power. All patients were diagnosed according to the American College of Rheumatology criteria revised in 1987. Informed consent was obtained from all subjects prior to participation in this study. Most patients had been previously treated with disease-modifying antirheumatic drugs (DMARDs), such as methotrexate (MTX), and prednisolone (PSL), and six patients had received anti-TNF agents, including infliximab (IFX) in three patients, adalimumab (ADA) in two patients and etanercept (ETN) in one patient. Based on the clinically inadequate responses to these previous treatments, the patients were recommended to receive treatment with biologics, such as anti-TNF agents and anti-interleukin-6 receptor antibodies. Whole-body ^{18}F -FDG PET/CT was performed at baseline, after which the patients were administered biological therapy, and again at six months after the start of treatment. Radiographs of the large joints were obtained at baseline and two years after the initiation of therapy.

Clinical parameters, including the erythrocyte sedimentation rate (ESR) and levels of C-reactive protein (CRP), matrix metalloproteinase-3 (MMP-3), anti-cyclic citrullinated peptide antibodies (ACPA) and rheumatoid factor (RF), were also assessed at baseline and six, 12 and 24 months after the initiation of biological therapy. The disease activity was evaluated at the same time using the disease activity score in 28 joints (DAS28), DAS28-CRP, simplified disease activity index (SDAI) and clinical disease activity index (CDAI).

PET imaging

After more than six hours of fasting, whole-body PET was completed following the intravenous injection of ^{18}F -FDG (5 MBq/kg). One hour after ^{18}F -FDG injection, the acquired data were conducted in 3-dimensional mode using a PET-CT scanner (Biograph 16; Siemens Medical Solutions Inc., Munich, Germany). The patients were placed in a supine position and scanned from the head to the toe in arms-down position. Attenuation correction of the PET images was done using CT and followed by reconstruction with an ordered subsets expectation-maximization algorithm into 128×128 matrices. The nuclear physicians with over fifteen years' experience interpreted the PET images. An increased FDG uptake in the bilateral shoulder, elbow, wrist, hip, knee and ankle joints was recorded as described below according to previous reports.^{12,13} The standardized uptake value (SUV) was calculated for the semiquantitative assessment by attenuation-corrected transaxial images, the injected dose of ^{18}F -FDG, patient's body weight and cross-calibration factor between the PET images and dose calibrator as follows.

$$\text{SUV} = \frac{\text{radioactive concentration in the region of interest (ROI) (MBq/g)}}{\text{injected } ^{18}\text{F-FDG dose (MBq)/patient's body weight (g)}}$$

At first the upper limit SUV was set as 5, the SUV images were observed. Then ROIs were manually drawn for each joint by a nuclear physician with the assistance of corresponding

CT scans. If there was high FDG uptake over $SUV_{max} > 5$, the upper limit SUV was set as 8 or 10. To assess of the FDG uptake, the maximum SUV (SUV_{max}) in the ROI was considered as a representative value of the FDG uptake.

Joint destruction assessment

Standard anteroposterior plain radiographs of the large joints (shoulder, elbow, wrist, hip, knee and ankle) were used. The hip and ankle joints were exposed in the supine position, and the knee joints were exposed under conditions of weight bearing. Radiographs of the large joints were taken at baseline and two years later. Joints that had previously been treated with joint replacement surgery at baseline were excluded from the radiographic assessments. A history of total joint replacement within two years was regarded as being indicative of joint destruction progression. Two certified rheumatologists (K.O. and Y.Y.) assessed the degree of joint damage in consultation with each other according to the method of Larsen et al.¹⁵ using standard reference films, without any information regarding the patients.

Statistics

The statistical analyses were conducted using the SPSS Statistics 22 statistical

analysis software program. The data are reported as the mean \pm standard deviation (SD). Group differences in disease duration, baseline disease characteristics (ESR, CRP, MMP-3, ACPA and RF), disease activity (DAS28, DAS28-CRP, SDAI and CDAI) and SUV were analyzed using the Mann-Whitney *U* test. A logistic regression analysis was performed to determine the factors most significantly contributing to the progression of joint destruction within two years. P values of < 0.05 were considered to be statistically significant.

Results

The main clinical and laboratory characteristics are provided in Table 1. The mean age of the patients was 66.9 years, and the mean duration of RA was 13.8 years. IFX was used in four patients, ETN was used in four patients and ADA was used in six patients. Tocilizumab (TCZ) was used in nine patients, including three patients switched from IFX, two patients switched from ADA and one patient switched from ETN due to side effects or a clinically inadequate response to the previous treatment. We assessed 12 large joints (bilateral joints of the shoulder, elbow, wrist, hip, knee and ankle) per patient, for a total of 276 joints. Twelve joints had previously been treated with joint replacement surgery at baseline and were excluded from the analysis. Therefore, we evaluated 264 large joints in this study.

Among the 264 joints in the patients with RA, radiographic progression of joint

destruction was detected in 33 large joints (shoulder/ elbow/ wrist/ hip/ knee/ ankle: 7/ 1/ 1/ 4/ 12 / 8), including four joints treated with surgery.

Figure 1 shows typical ^{18}F -FDG PET/CT images of large joints exhibiting arthritis in RA patients. A 63-year-old female with a 32-year history of RA received TCZ therapy, and her left knee joint subsequently demonstrated progression of joint damage within two years (Larsen grade change from III to IV). The SUVmax in the left knee was 5.19 at baseline and 3.36 at six months (Fig.1a-d).

A 70-year-old female with a three-year history of RA was treated with IFX therapy. Her grade II left wrist showed progression to grade III; the SUVmax in the left wrist was 1.73 at baseline and 2.54 at six months (Fig.1e-h).

The background characteristics of the patients with and without radiographic progression over two years were evaluated. The SUV values at baseline and six months and the ΔSUV , the difference in the SUVmax of the joints before and after treatment, were also assessed between these two groups (Table 2).

There were no significant differences between the groups with and without radiographic progression with respect to the following characteristics: laboratory values at baseline (CRP, MMP-3, ACPA), DAS28-ESR at baseline, DAS28-CRP, SDAI and CDAI. The disease duration, ESR level and RF level at baseline were significantly higher in the group with radiographic progression of joint damage ($p = 0.05$, $p = 0.002$ and $p = 0.006$).

Furthermore, the DAS28-ESR scores at six, 12 and 24 months were also significantly higher in the group with progression of joint destruction ($p = 0.006$, $p = 0.007$ and $p = 0.008$).

Regarding the ^{18}F -FDG PET/CT findings, the statistical analyses revealed that the SUVmax values at baseline and six months were significantly higher in the group with progressive joint destruction ($p = 0.006$ and $p = 0.021$) (Fig.2). As for the ΔSUVs , which represent clinical improvements in the affected joints over six months, there were no significant differences between the patients with radiographic progression of joint destruction at two years and those without progression.

The disease duration, DAS28-ESR scores at six, 12 and 24 months, SUVmax values at baseline and six months, which were found to be significant variables in the univariate analyses, as well as age and sex were entered simultaneously into a stepwise multivariate logistic regression analysis to identify factors with independent predictive value for joint destruction within two years. The analysis revealed that the SUVmax at baseline and DAS28-ESR at six months were factors associated with joint destruction at two years (Odds ratio (OR) 1.350, 95% confidence interval (CI): 1.013 – 1.798 and OR 1.954, 95%CI: 1.375 - 2.779, respectively).

Discussion

The findings of assessments of radiographic damage in large joints in comparison with that observed in small joints have been reported only in a limited number of studies. However, it is well recognized that RA affects large joints at an incidence of 21-56% during the disease process.¹⁶ Kuper et al. found that, after six years of follow-up, 50% of RA patients demonstrated radiographic abnormalities in at least one large joint,⁷ and radiographic damage of the large joints in the setting of RA substantially contributes to physical disability, with a negative effect on the quality of life of the patient.^{7,8}

Drossaers-Bakker et al. reported similar correlations between radiographic damage of the large and small joints associated with disability. The authors found the disease activity and radiographic damage of the large joints to be main contributors to variation in the Health Assessment Questionnaire (HAQ) scores in a multivariate analysis.⁸ In addition, Tanaka et al. reported that damage to large joints, especially the shoulder, elbow and knee, is the major determinant of the RA disease activity, as assessed according to a patient-oriented evaluation of pain using a visual analog scale (VAS), the patient's and physician's general VAS and the HAQ.¹⁷ Therefore, it is important to assess the extent of joint destruction of large joints in RA patients.

Over the past decade, new imaging modalities, such as magnetic resonance imaging (MRI) and ultrasonography (US), have been established to assess the degree of

synovitis in RA-affected joints. MRI has become an important modality due to its ability to visualize synovial inflammation as contrast-enhanced lesions, especially in the wrist and finger joints. However, RA often affects large joints throughout the entire body, and MRI is currently not effective for assessing multiple distant joints or misfits with metallic implants. US has been reported to be more sensitive and reliable than physical examinations in detecting synovial hypertrophy, effusion and inflammation.¹⁸ Although US examinations are cheap and widely available, the results have been shown to be observer-dependent.

In the present study, whole-body ¹⁸F-FDG PET/CT was performed at baseline and six months after the initiation of the biological therapy in patients with RA. Whole-body imaging with FDG-PET appears to be a more objective method of assessment. Furthermore, the SUV is highly correlated with the synovial thickness measured on US and MRI.^{9,10} Kubota et al. reported the FDG uptake in large joints to be significantly correlated with the CRP level, and a greater FDG uptake was observed in painful/swollen joints. The authors suggested that FDG-PET can be used to identify joints with active RA inflammation more sensitively than clinical signs/symptoms of RA.⁶ Therefore, we performed ¹⁸F-FDG PET/CT to assess large joints in RA patients before and after biological therapy in this study.

In the current study, higher levels of SUVmax at baseline and six months after the initiation of biological therapy were observed in the 33 large joints in which

radiographic progression of joint destruction was detected. Because the Δ SUV represents the changes in the clinical status of the affected joints at six months, one of our hypotheses is that a low Δ SUV leads to joint destruction. However, there were no significant differences in the Δ SUV values between the patients with and without joint destruction at two years.

On the other hand, the SUVmax values at baseline and six months and the DAS28-ESR scores at six months in the joint destruction progression group were significantly high in this study. These results suggest that determining the disease activity for the entire body, as well as for a single joint, is therefore important to avoid joint destruction of the large joints within two years, especially in RA patients with joints exhibiting high SUVmax levels at the initiation of biological therapy. In other words, RA patients with a high disease activity should be treated as soon as possible, as the continuation of a high disease activity may contribute to further joint destruction. Previous studies also suggest that early intervention aimed at preventing radiographic damage before or at the onset of minor radiographic changes may help to preserve the joint function.⁷⁻¹⁹

There are some limitations associated with this study. First there is concern regarding radiographic assessments performed using the Larsen grade. In this method, various changes are included within one grade. Therefore, the Larsen score discriminates changes poorly in cases in which the changes in radiographic abnormalities are mild. In

addition, it may be difficult to distinguish joint destruction caused by RA from secondary osteoarthritis in large joints detected progression of joint damage with Larsen method. On this point, further research is important in order to evaluate large joints more precisely using other radiographic scoring systems.

Second is the problem with the follow-up term. A previous study reported that 18% of patients had already developed damage in at least one large joint (Larsen ≥ 1) at baseline, without a preference for a specific joint. Within three years, 40% of the patients and, within six years, almost 50% of the patients showed radiographic changes, especially in the hips, knees and shoulders.⁷ Furthermore, another study demonstrated that only 30% of the studied patients exhibited no radiographic abnormalities of the large joints after 12 years of follow-up.⁸ On the other hand, Seki et al. reported that 6% of large joints in patients with RA showed progression of joint damage after one year of treatment with TNF-blocking therapy.¹⁹ In the current study, 12% of the patients developed radiographic changes after two years. These results support the idea that two years may be too short a period to properly evaluate radiographic changes in large joints, and further long-term observation is thus required.

Third is the difference in the treatments for each patients. Because each patients had been treated with several DMARDs, there was a possibility that these drugs interfered with clinical parameters and imaging data in this study.

In conclusion, we investigated the associations between destruction of the large joints in RA patients and ^{18}F -FDG PET/CT findings, the disease activity and laboratory parameters after biological treatment and identified factors associated with joint destruction at two years. In particular, the FDG uptake at baseline and six months and the disease activity at six, 12 and 24 months were significantly higher in the large joints demonstrating radiographic progression of destruction at two years after the initiation of biological therapy. Furthermore, the SUVmax at baseline and DAS28–ESR at six months after biological treatment are significant factors predicting joint destruction of the large joints at two years.

Conflict of interest: The authors have no conflicts of interest to declare.

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Figure legends

Figure 1: Typical ^{18}F -FDG PET/CT images and radiographs with a progression of joint destruction

A 63-year-old female with a 32-year history of RA treated with TCZ therapy. Anterior image obtained on ^{18}F -FDG PET/CT at baseline (a) and six months after the initiation of biological therapy (b). The Larsen grade in the left knee joint progressed from grade III (c) to grade IV (d).

A 70-year-old male with a three-year history of RA treated with IFX therapy. ^{18}F -FDG PET/CT findings at baseline and six months after treatment (e, f). The Larsen grade in the left wrist progressed from grade II to grade III (g, h).

Progression of joint destruction was shown in the joints with high FDG uptake at baseline and six months.

FDG-PET/CT: ^{18}F -fluorodeoxyglucose positron emission tomography combined with computed tomography

Figure 2: SUVmax values in the joints with and without radiographic progression

(a) SUVmax values at baseline. The SUVmax values were significantly higher in the joints with radiographic progression than in the joints without radiographic progression ($p = 0.006$). (b) SUVmax values at six months. The SUVmax values were significantly higher in

the joints with radiographic progression than in the joints without radiographic progression

($p = 0.021$).

SUVmax: maximum standardized uptake value

Table 1. Baseline demographic, clinical and laboratory features of the 23 patients

Baseline characteristics	Values
Age (years)	66.9 ± 7.9
Sex (Male/Female)	6/17
Steinbrocker stage (I/ II/ III/ IV)	1/ 1/ 10/ 11
Steinbrocker class (1/ 2/ 3/ 4)	2/ 10/ 5/ 6
Biologics (ADA/ ETN/ IFX/ TCZ)	6/ 4/ 4/ 9
Disease duration (years)	13.8 ± 12.8
WBC (/μL)	6580 ± 1960
ESR (mm/h)	63.4 ± 30.0
CRP (mg/dl)	2.15 ± 2.73
MMP-3 (ng/ml)	271 ± 247
ACPA (U/ml)	96.3 ± 100.6

RF (U/ml)	293 ± 839
DAS28-ESR	5.19 ± 1.09
DAS28-CRP	4.23 ± 1.12
SDAI	23.0 ± 13.8
CDAI	20.8 ± 12.6

The data are presented as the mean ± standard deviation (SD), WBC : white blood cell, ESR : erythrocyte sedimentation rate, CRP : C-reactive protein, MMP-3 : matrix, metalloproteinase-3, ACPA: anti-cyclic citrullinated peptide antibody, RF : rheumatoid factor, DAS28 : disease activity score in 28 joints, SDAI : simplified disease activity index, CDAI : clinical disease activity index, ADA : adalimumab, ETN : etanercept, IFX : infliximab, TCZ : tocilizumab

Table 2. Parameters contributing to the radiographic progression of large joint destruction

Variable	No radiographic progression joints (n=230)	Radiographic progression joints (n=33)	p value
disease duration (years)	12.7 ± 12.3	20.8 ± 14.7	0.005*
Larsen grade at baseline (0/ I / II/ III/ IV/ V)	0/ 22/ 94/ 55/ 56/ 4	0/ 6/ 6/ 16/ 5/ 0	0.821
WBC (/μL)	6650 ± 1930	6610 ± 2220	0.792
ESR (mm/h)	60.9 ± 29.8	79.4 ± 26.3	0.002*
CRP (mg/dl)	2.06 ± 2.58	3.13 ± 3.65	0.101
MMP-3 (ng/ml)	271.7 ± 243.9	314.5 ± 290.5	0.576
ACPA (U/ml)	100.0 ± 103.5	84.1 ± 93.9	0.8
RF (U/ml)	230.2 ± 717.6	737 ± 1386	0.006*

DAS28-ESR			
at baseline	5.16 ± 1.06	5.41 ± 1.17	0.126
6 months	2.99 ± 1.22	3.86 ± 1.46	0.004*
12 months	3.26 ± 1.67	4.05 ± 1.39	0.007*
24 months	2.82 ± 1.27	3.55 ± 1.43	0.008*
DAS28-CRP	4.23 ± 1.09	4.35 ± 1.31	0.448
SDAI	23.0 ± 13.8	23.9 ± 13.9	0.648
CDAI	20.9 ± 12.6	20.5 ± 12.5	0.73
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FDG-PET findings			
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SUV at baseline	2.21 ± 1.38	2.66 ± 1.15	0.006*
SUV at 6months	1.89 ± 0.98	2.15 ± 0.77	0.021*
ΔSUV			
6 months – baseline	- 0.32 ± 1.25	- 0.51 ± 0.92	0.087

The data are presented as the mean (S.D.).

*indicates a significant difference between joints with and without radiographic progression ($p < 0.05$).

FDG-PET: ^{18}F -fluorodeoxyglucose positron emission tomography

SUV: standardized uptake value

Figure 1. Typical FDG-PET/CT images and radiographs with a progression of joint destruction



Figure 2. SUVmax values in the joints with and without radiographic progression



