The assessment of biologic treatment in patients with rheumatoid arthritis using FDG-PET/CT

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Abstract

Objectives. To evaluate whether there is a correlation between the differences in joint uptake of 2-[18F]-fluoro-2-deoxy-D-glucose (18F-FDG) and the improvement of clinical findings in RA patients undergoing anti-TNF therapies.

Methods. Twenty-two patients who received anti-TNF therapies, including infliximab for 16 patients and etanercept for 6 patients, were assessed. PET with 18F-FDG studies and clinical assessments were performed at baseline and 6 months after the initiation of therapy. The maximal standardized uptake value (SUVmax) was used as a representative value for the assessment of the FDG uptake in the bilateral shoulder, elbow, wrist, hip, knee and ankle joints. Spearman's rank correlation test was applied to assess the correlation between the SUV and the clinical parameters.

Results. The ΔSUV (12 joints), the difference in the SUVmax of the affected 12 joints before and after treatment, was positively correlated with the ΔDAS28 (r = 0.609, P = 0.003), ΔDAS28-CRP (r = 0.656, P = 0.001) and Δtender joint count (TJC) (r = 0.609, P = 0.003). There were also significantly positive correlations between ΔSUV (8 joints); the difference in the SUVmax of the bilateral shoulder, elbow, wrist and knee joints before and after treatment and the ΔDAS28 (r = 0.642, P = 0.001), ΔDAS28-CRP (r = 0.712, P < 0.001) and ΔTJC (r = 0.608, P = 0.003), respectively.

Conclusion. The FDG uptake observed in the inflamed RA joints may reflect disease activity. The FDG-PET response was correlated with the clinical response to the biologic treatment of RA.

Key words: rheumatoid arthritis, anti-TNF, FDG-PET, SUV, disease activity, treatment response.

Introduction

The main pathological manifestations of RA include synovitis, pannus formation and bone erosion. These pathological changes are usually assessed by plain X-ray, US, CT and contrast-enhanced, fat-suppressed MRI. PET with 2-[18F]-fluoro-2-deoxy-D-glucose (18F-FDG) can be used to evaluate the metabolic activity of synovitis and measure the disease activity in RA patients by whole-body imaging [1-4].

Imaging studies using 18F-FDG-PET have been performed to assess the metabolic activity of synovitis in patients with RA and to evaluate the disease activity of RA [5-11]. Several reports have indicated that there was a significant correlation between the visual assessment of FDG uptake, i.e. the visual uptake score and clinical evaluation of disease activity [6, 9]. Furthermore, PET findings have been correlated with MRI and US assessments of the pannus in patients with RA [3-5] as well as with the classical serum parameter of inflammation, CRP and the synovium-derived parameter, serum MMP-3 [3].

Recent advances in medical biology and pharmaceutical engineering have provided new drugs, such as TNF inhibitors, anti-IL-6 receptor antibodies and anti-CD20 antibodies for the treatment of RA patients [12]. Clinical application of novel therapies for RA has stimulated increased interest in the radiological assessment of the
disease activity. Since an incomplete response leads patients who have been undergoing these biologic therapies to discontinue the treatment, which has high costs and possible side effects, monitoring of the specific biologic response to the therapies might be helpful for the clinicians to determine suitable treatments. Therefore, the development of molecular imaging methods would be beneficial, especially in RA patients.

One of the merits of PET is that it enables quantitative measurement of metabolic activity. $^{18}$F-FDG-PET studies have been proposed to assess the metabolic activity measured quantitatively by the standardized uptake value (SUV) of articular lesions in patients with RA. In the present study we evaluated whether the FDG uptake of the affected joints represented by the SUV correlated with the clinical assessment of patients with RA. In addition, we evaluated if there was a correlation between the differences in the SUV and the improvement of the clinical findings in RA patients receiving anti-TNF therapies.

### Materials and methods

#### Patients and methods

The institutional review board of the hospital approved the study, and informed consent was obtained from each patient. Twenty-two patients [2 males, 20 females; average age 57.3 (20–74) years] were enrolled in this study. All patients were diagnosed according to the ACR criteria revised in 1987 [13] and their previous treatment with DMARDs including MTX provided clinically inadequate responses. Hence the patients were recommended for treatment with anti-TNF agents [infliximab (IFX) for 16 patients and etanercept (ETN) for 6 patients]. The average disease duration of these patients was 13.2 (1–49) years. The average dose of MTX for the 22 patients was 5.1 mg/week, and the average dose of prednisolone (PSL) was 2.9 mg/day (Table 1). After the baseline assessment using whole-body $^{18}$F-FDG-PET/CT (FDG-PET/CT), they underwent the biologic therapies. The FDG-PET and clinical assessments were also performed 6 months after the initiation of the therapies. Clinical assessments included ESR, serum concentrations of CRP, MMP-3 and RF. The activity of inflammation was evaluated using both the DAS28 and the DAS28-CRP. The DAS28 was calculated based on the results of the 28 tender joint count (TJC), 28 swollen joint count (SJC) and ESR. The DAS28-CRP was calculated using the TJC, SJC and CRP. For the calculation of the DAS28 and DAS28-CRP scores, the following formulas [14] were used:

$$\text{DAS28} = 0.56 \times \sqrt{\text{TJC}28} + 0.28 \times \sqrt{\text{SJC}28} + 0.70 \times \ln(\text{ESR}) \times 1.08 + 0.16,$$

$$\text{DAS28-CRP} = 0.56 \times \sqrt{\text{TJC}28} + 0.28 \times \sqrt{\text{SJC}28} + 0.36 \times \ln(\text{CRP} + 1) \times 1.10 + 1.15$$

Clinical improvement was assessed by the changes in the DAS28 after the therapy according to the European League Against Rheumatism (EULAR) response criteria [15].

#### PET images

Whole-body PET was performed following i.v. injection of $^{18}$F-FDG (5 MBq/kg) after the patient had fasted for >6 h. Data acquisition was done in 3D mode 60 min after the injection using a PET-CT scanner (Biograph 16; Siemens Medical Solutions Inc., Munich, Germany). Patients were scanned from the head to the toe in the arms-down position. Attenuation correction of the PET images was performed using CT, followed by reconstruction using an ordered subsets expectation-maximization algorithm into 128 × 128 matrices. PET images were interpreted by experienced nuclear physicians, and increased FDG uptake in bilateral shoulder, elbow, wrist, hip, knee and ankle joints was recorded. We selected these joints for the evaluation of the FDG uptake because these joints were suitable for the clinical assessment of RA patients. These large joints needed no additional or separate scanning or the use of auxiliary devices, such as those needed for the scanning of finger lesions, which reduces the burden for patients. In addition, the easy-to-use area settings lead to decreased intra- and interobserver differences for nuclear physicians.

#### Data analysis

For the semiquantitative analysis, functional images of the SUV were produced using attenuation-corrected transaxial images, the injected doses of FDG, the patient’s body weight and the cross-calibration factor between PET and dose calibrator. The SUV was defined as follows:

$$\text{SUV} = \frac{\text{radioactive concentration in the region of interest (ROI)} \times \text{(MBq/g)/injected dose (MBq)/patient’s body weight}}.$$
ROIs were manually drawn at each joint on the SUV images. The ROI analysis was conducted by a nuclear physician with the aid of corresponding CT scans. The maximal SUV in the ROI was used as a representative value for the assessment of the FDG uptake. For assessment of therapeutic response, the clinical parameters DAS28, DAS28-CRP, ESR, CRP, MMP-3 and RF were obtained at the same time as the PET study. The therapeutic response was evaluated by the changes in the mean value of the maximal SUV of the affected joints (mean SUV) and the DAS28. We used all 12 joints evaluated by FDG-PET or 8 (bilateral shoulder, elbow, wrist and knee) joints which were represented in the DAS28 for the calculation of the average SUVmax. The $\Delta$SUV, $\Delta$DAS28 and $\Delta$DAS28-CRP ($\Delta$DAS28-CRP) were defined as follows:

$$\Delta$$SUV = meanSUV$_{pre}$ – meanSUV$_{6m}$,

$$\Delta$$DAS28 = DAS28$_{pre}$ – DAS28$_{6m}$,

$$\Delta$$DAS28-CRP = DAS28-CRP$_{pre}$ – DAS28-CRP$_{6m}$

In the above formula, the meanSUV$_{pre}$, meanSUV$_{6m}$, DAS28$_{pre}$, DAS28$_{post}$, DAS28-CRP$_{pre}$ and DAS28-CRP$_{6m}$ represent the mean SUV at baseline, the mean SUV after treatment, the DAS28 at baseline, the DAS28 after treatment, the DAS28-CRP at baseline and the DAS28-CRP after treatment for each patient. In the following result section, $\Delta$ indicates the difference in the values before and after treatment.

**Statistical analysis**

The treatment responses were evaluated on both a patient and a joint basis. Wilcoxon’s signed rank sum tests were used to assess the differences in the evaluations of the treatment. Spearman’s rank correlation test and the partial correlation analyses were applied to test for correlations of the different parameters recorded in this study. The IBM SPSS Statistics 19 software program (International Business Machines Corp., New York, NY, USA) was used for the analysis. $P < 0.05$ was considered to be statistically significant. For multiple correlations we used Bonferroni’s correction [16], and the significance of correlation coefficients was calculated.

**Results**

PET-CT images of a typical case, both prior to therapy and at the follow-up examination, are provided in Fig. 1. Before treatment, the averages of the measured parameters were as follows: DAS28 5.29 ± 1.01 (3.47–6.95), DAS28-CRP 4.33 ± 1.06 (2.39–6.28), ESR (mm/h) 68.7 ± 27.9 (18.0–111.0), CRP (mg/dl) 2.69 ± 2.81 (0.15–11.30), MMP-3 (ng/ml) 342.6 ± 326.4 (46.6–1206.1), RF (IU/ml) 85.4 ± 129.2 (10.0–549.0), TJC 5.4 ± 4.3 (0–17), SJC 7.0 ± 5.0 (2–19), SUV (12 joints) (the average of SUV$_{max}$ among the measured 12 joints per patient) 2.14 ± 0.55 (1.14–3.12), SUV (8 joints) (the average of SUV$_{max}$ among bilateral shoulder, elbow, wrist and knee joints per patient) 2.24 ± 0.64 (1.19–3.28) (Table 2).

Six months after the initiation of anti-TNF therapies, the average observed values were as follows: DAS28 3.81 ± 0.86 (2.21–5.33), DAS28-CRP 2.65 ± 0.91 (1.19–4.09), ESR (mm/h) 46.8 ± 26.3 (14.0–107.0), CRP (mg/dl) 0.92 ± 1.77 (0.01–8.33), MMP-3 (ng/ml) 168.3 ± 199.9 (22.3–884.9), RF (IU/ml) 54.2 ± 65.6 (8.0–269.0), TJC 1.2 ± 1.2 (0–4), SJC 2.1 ± 2.1 (0–7), SUV (12 joints) 1.66 ± 0.48 (0.94–2.62) and SUV (8 joints) 1.72 ± 0.54 (0.82–2.80) (Table 2).

We evaluated the responses of the RA patients to these therapies based on the FDG-PET/CT results and the clinical parameters. The values of all disease parameters were significantly decreased after biologic treatment compared with baseline (Table 2).

We next performed the joint-based analyses for the 12 or 8 joints of each of the 22 RA patients. We evaluated the changes in the existence of the tender joints and swollen joints. Additionally, the SUV of the affected joints before and after the biologic treatments were assessed for each joint in each patient. The tenderness of the joints in the right shoulder, left wrist and right knee were significantly decreased after the biologic treatment. The swollen joints of bilateral elbows and bilateral wrists were also found to be decreased after treatment when evaluated on an individual joint basis. The SUV of the left shoulder, right elbow, bilateral wrists, bilateral knees, right hip and right ankle were decreased compared with the SUV at baseline in each patient (Table 3).

At baseline the SUV (12 joints) was correlated with the TJC ($r = 0.578, P = 0.005$). The SUV (8 joints) was correlated with the DAS28 ($r = 0.588, P = 0.004$), DAS28-CRP ($r = 0.712, P = 0.003$) and TJC ($r = 0.621, P = 0.002$) (Table 4).

Six months after treatment the SUV (12 joints) was correlated with the DAS28 ($r = 0.577, P = 0.005$), DAS28-CRP ($r = 0.568, P = 0.006$) and ESR ($r = 0.623, P = 0.002$). The SUV (8 joints) was correlated with the DAS28 ($r = 0.602, P = 0.003$), DAS28-CRP ($r = 0.597, P = 0.003$), ESR ($r = 0.580, P = 0.005$) and SJC ($r = 0.567, P = 0.006$) (Table 4).

The $\Delta$SUV (12 joints), the difference in the SUV$_{max}$ of the 12 affected joints before and after treatment, was significantly correlated with the $\Delta$DAS28 ($r = 0.609, P = 0.003$), $\Delta$DAS28-CRP ($r = 0.656, P = 0.001$) and $\Delta$TJC ($r = 0.609, P = 0.003$). There was no correlation between the $\Delta$SUV (12 joints) and $\Delta$MMP-3 after Bonferroni’s correction ($r = 0.499, P = 0.018$). The $\Delta$ESR ($r = 0.412, P = 0.057$), $\Delta$CRP ($r = 0.340, P = 0.121$), $\Delta$RF ($r = 0.149, P = 0.507$) and $\Delta$SJC ($r = 0.222, P = 0.320$) did not correlate with the $\Delta$SUV (12 joints) (Table 4).

There were also significant correlations between the $\Delta$SUV (8 joints), the difference in the SUV$_{max}$ of the bilateral shoulder, elbow, wrist and knee joints before and after treatment and the $\Delta$DAS28 ($r = 0.642, P = 0.001$), $\Delta$DAS28-CRP ($r = 0.712, P < 0.001$) and $\Delta$TJC ($r = 0.608, P = 0.003$), respectively (Table 4).

We also used partial correlation coefficients to examine whether the $\Delta$CRP or $\Delta$ESR had any effect on the correlations between the $\Delta$SUV and $\Delta$DAS28 or $\Delta$DAS28-CRP.
Fig. 1 A 60-year-old female with a 10-month history of RA.

(A) Whole-body $^{18}$F-FDG-PET/CT was performed before anti-TNF therapy (IFX). (B) Six months after initiation of therapy FDG uptake of the affected joints (circles) had decreased.

*Table 2* Parameters for all patients before and after treatment

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Before treatment</th>
<th>After treatment</th>
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<tbody>
<tr>
<td>DAS28</td>
<td>5.29 (1.01) (3.47–6.95)</td>
<td>3.81 (0.86) (2.21–5.33)**</td>
</tr>
<tr>
<td>DAS28-CRP</td>
<td>4.33 (1.06) (2.39–6.28)</td>
<td>2.65 (0.91) (1.19–4.09)***</td>
</tr>
<tr>
<td>ESR, mm/h</td>
<td>68.7 (27.9) (18.0–111.0)</td>
<td>46.8 (26.3) (14.0–107.0)**</td>
</tr>
<tr>
<td>CRP, mg/dl</td>
<td>2.89 (2.81) (0.15–11.30)</td>
<td>0.92 (1.77) (0.01–8.33)**</td>
</tr>
<tr>
<td>MMP-3, ng/ml</td>
<td>342.6 (326.4) (46.6–1206.1)</td>
<td>168.3 (199.9) (22.3–884.9)**</td>
</tr>
<tr>
<td>RF, IU/ml</td>
<td>85.4 (129.2) (10.0–549.0)</td>
<td>54.2 (65.6) (8.0–269.0)*</td>
</tr>
<tr>
<td>Tender joints</td>
<td>5.4 (4.3) (0–17)</td>
<td>1.2 (1.2) (0–4)***</td>
</tr>
<tr>
<td>Swollen joints</td>
<td>7.0 (5.0) (2–19)</td>
<td>2.1 (2.1) (0–7)***</td>
</tr>
<tr>
<td>SUV (12 joints)</td>
<td>2.14 (0.55) (1.14–3.12)</td>
<td>1.66 (0.48) (0.94–2.62)**</td>
</tr>
<tr>
<td>SUV (8 joints)</td>
<td>2.24 (0.64) (1.19–3.28)</td>
<td>1.72 (0.54) (0.82–2.80)**</td>
</tr>
</tbody>
</table>

Data are given as mean (s.d.) (range). The average of each parameter was calculated before and after treatment. All disease parameters were significantly decreased after biologic treatment. *$P<0.05$, **$P<0.005$ and ***$P<0.001$, indicating significant differences compared with the parameters at baseline.
When CRP was the control variable, there were partial correlations between the \(\Delta\text{SUV} \) (12/8 joints) and the \(\Delta\text{DAS28} \) (Table 5). There were also partial correlations between the \(\Delta\text{SUV} \) (12/8 joints) and the \(\Delta\text{DAS28-CRP} \) when ESR was the control variable (Table 5).

### Discussion

The results of this study indicated that the total \(\text{SUV}_{\text{max}} \) closely correlated with the disease activity of RA. Kubota et al. [9] demonstrated that the visual FDG uptake score
TABLE 5 The partial correlations between the ΔSUV (12 joints)/ΔSUV (8 joints) and the changes in the clinical findings

<table>
<thead>
<tr>
<th>Control variable</th>
<th>ΔDAS28</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔCRP</td>
<td></td>
</tr>
<tr>
<td>ΔSUV (12 joints)</td>
<td>r 0.558</td>
</tr>
<tr>
<td>P</td>
<td>0.009</td>
</tr>
<tr>
<td>ΔSUV (8 joints)</td>
<td>r 0.511</td>
</tr>
<tr>
<td>P</td>
<td>0.018</td>
</tr>
<tr>
<td>ΔESR</td>
<td></td>
</tr>
<tr>
<td>ΔSUV (12 joints)</td>
<td>r 0.534</td>
</tr>
<tr>
<td>P</td>
<td>0.013</td>
</tr>
<tr>
<td>ΔSUV (8 joints)</td>
<td>r 0.493</td>
</tr>
<tr>
<td>P</td>
<td>0.023</td>
</tr>
</tbody>
</table>

When the ΔCRP was the control variable, there were partial correlations between the ΔSUV (12/8 joints) and the ΔDAS28. There were partial correlations between the ΔSUV (12/8 joints) and the ΔDAS28-ΔCRP when ΔESR was the control variable.

While SUVs correlated with the clinical status of the patients, the SUVs noted above were based on monarthritic assessments, and none of the previous reports simultaneously evaluated multiple joints throughout the body to assess the clinical condition or treatment responses of the patients. Therefore, in this study, to provide a semiquantitative analysis and to focus on the potential utility of FDG-PET in clinical practice, we conducted whole-body FDG-PET/CT and used the SUV$_{\text{max}}$ to determine the FDG uptake.

The difference in the mean SUV$_{\text{max}}$ between studies before and after anti-TNF therapies might reflect the changes in the disease activity resulting from the medication, because these values were significantly correlated with the differences in the DAS28 and DAS28-CRP in this study. Goerres et al. [6] assessed seven RA patients prior to and 12 weeks after IFX treatment using FDG-PET imaging-based total joint scores and concluded that visual assessment of the FDG uptake showed a significant correlation with the clinical evaluation of disease activity performed by the rheumatologist in patients undergoing anti-inflammatory treatment.

In a previous study, Kubota et al. [9] indicated that the total SUV$_{\text{max}}$ and the CRP levels were weakly, but not significantly, correlated. In our study, the CRP levels at baseline and after treatment were not significantly correlated with the total SUV$_{\text{max}}$, and the ΔCRP was not significantly correlated with the ΔSUV. On the other hand, Beckers et al. [10] demonstrated in 16 rheumatoid knees that the SUVs were significantly correlated with serum CRP levels at baseline and that the changes in the SUVs after TNF therapy were also correlated with changes in serum CRP levels. The reason why the CRP did not correlate with the total SUV may be that the CRP in itself cannot reflect the whole-body disease activity of RA patients. Since the CRP tends to mirror the swelling of the larger joints of the human body, the FDG uptake of the knee, one of the largest joints, might correlate best with the serum CRP levels. Further evaluation is needed to assess the relationship between the CRP and the SUVs.

Another question to be answered was whether FDG-PET detects subclinical arthritis better than MRI. MRI is sensitive for depicting morphological changes by estimating the pannus volume or synovial thickness in the early stage of the disease. An early and accurate diagnosis is the key to optimal treatment in patients with RA. However, these studies are limited to morphologically based information. Furthermore, high-resolution, contrast-enhanced MRI is limited to circumscribed areas of the body. Beckers et al. [3] demonstrated that PET-positive knees exhibited significantly higher SUVs, higher MRI parameters and greater synovial thicknesses compared with PET-negative knees, whereas the serum CRP and MMP-3 levels were not significantly different. Additionally, Kubota et al. [9] suggested that FDG-PET could identify joints with active RA inflammation more sensitively than monitoring the clinical
signs/symptoms of RA. Therefore, FDG-PET might be more suitable for the detection of subclinical arthritis than other modalities.

We hypothesized that FDG-PET would be able to detect a clinical response in both patients with RA and in their individual joints. In this study, we compared the changes in the SUVs with the clinical response of the patients and the tender/swollen joints to biologic treatments 6 months after initiating the treatment. As a result, the SUV and patients’ disease status were found to be significantly decreased compared with the baseline. These effects were due to the 6 months of treatment. Biologic therapies usually exert a rapid effect against RA, and can sufficiently reduce disease activity 6 months after the initiation of treatment. Although therapeutic effects on the left shoulder, left knee, right hip and right ankle joints were not clinically detectable, the SUVs of the joints were still significantly decreased compared with the baseline in each patient. Our data indicated that the FDG-PET might be sensitive to the changes of tender/swollen joints to detect the responses of the biologic treatment. Further cross-sectional and longitudinal studies are needed before 18F-FDG-PET can be considered one of the qualitative clinical evaluation technologies for the assessment of therapeutic effects in RA patients.

In the present study, the SUV was closely correlated with the disease activity of RA; however, the precise pathological condition of RA reflected by the 18F-FDG-PET has not been understood. It has been reported that pro-inflammatory cytokines such as TNF-α and hypoxia might contribute to the 18F-FDG uptake by cells involved in pannus formation in RA [17]; therefore, the 18F-FDG accumulation in RA patients may reflect the proliferation of the pannus and inflammatory activity. The disease activity and FDG uptake were significantly correlated in the present study, and these findings were consistent with a previous study [6, 9]. In the clinical examination of RA patients, because metabolic changes are likely to precede morphological changes, that is to say, the activated synovitis directly lead to the future joint destruction, 18F-FDG-PET accumulation may provide important biologic information for the rheumatologist to ensure strict disease control in RA patients.

The limitations of this study were the small number of patients and the number of assessed joints. The FDG-PET/CT instruments were only introduced in limited facilities, which restricted the number of examinations that could be performed. Further investigation is needed to assess the inflammation of RA joints. With regard to the radiation given to the RA patients, we made a dose reduction by the CT-based attenuation correction method, which reduced the radiation dose levels because the tube current was lower than that used for diagnostic CT.

In conclusion, the FDG uptake observed in the inflamed RA joints can reflect the disease activity. FDG-PET might play an important role in the evaluation of the biologic treatment for RA.

**Rheumatology key messages**

- 18F-FDG-PET can image the extent of inflammation in patients with RA.
- The differences in SUVs may reflect the therapeutic effects of RA treatments.
- FDG-PET can be used to evaluate the response of RA patients to biologic treatment.

**Disclosure statement**: The authors have declared no conflicts of interest.

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16 Curtin F, Schulz P. Multiple correlations and Bonferroni’s correction. Biol Psychiatry 1998;44:775–7.