18F-FDG and 18F-NaF PET/CT demonstrate coupling of inflammation and accelerated bone turnover in rheumatoid arthritis

Toshiyuki Watanabe1, Kaoru Takase-Minegishi2, Atsushi Ihata3, Yosuke Kunishita2, Daiga Kishimoto2, Reikou Kamiyama4, Maasa Hama2, Ryusuke Yoshimi3, Yohei Kiriño5, Yukiko Asami2, Akiko Suda1, Shigeru Ohno1, Ukihide Tateishi4, Atsuhisa Ueda2, Mitsuhiro Takeno6, and Yoshiaki Ishigatsubo2

1Center for Rheumatic disease, Yokohama City University Medical Center, Yokohama, Japan; 2Department of Internal Medicine and Clinical Immunology, Yokohama City University Graduate School of Medicine, Yokohama, Japan; 3Department of Rheumatology and Infectious disease, Yokohama Minami Kyosai Hospital, Yokohama, Japan; 4Department of Radiology, Yokohama City University Graduate School of Medicine, Yokohama, Japan

Abstract

Objective. To compare the findings in rheumatoid arthritis (RA)-affected joints between 18F-fluorodeoxyglucose (FDG) and 18F-fluoride (NaF) positron emission tomography (PET)/computed tomography (CT).

Methods. We enrolled twelve RA patients who started a new biologic agent (naïve 9 and switch 3). At entry, both hands were examined by 18F-FDG PET/CT, 18F-NaF PET/CT, and X-ray. Intensity of PET signals was determined by standardized uptake value max (SUVmax) in metacarpophalangeal (MCP), proximal interphalangeal (PIP), and ulnar, medial, and radial regions of the wrists. Hand X-rays were evaluated according to the Genant-modified Sharp score at baseline and 6 months.

Results. Both 18F-FDG and 18F-NaF accumulated in RA-affected joints. The SUVmax of 18F-FDG correlated with that of 18F-NaF in individual joints (r = 0.65), though detail distribution was different between two tracers. 18F-NaF and 18F-FDG signals were mainly located in the bone and the surrounding soft tissues, respectively. The sum of SUVmax of 18F-NaF correlated with disease activity score in 28 joint (DAS28), modified health assessment questionnaire (MHAQ), and radiographic progression. 18F-FDG and 18F-NaF signals were associated with the presence of erosions, particularly progressive ones.

Conclusion. Our data show that both 18F-FDG and 18F-NaF PET signals were associated with RA-affected joints, especially those with ongoing erosive changes.

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by autoimmunity and polyarticular synovial inflammation; subsequently, there is destruction of cartilage and bone. The earliest bone change detected by X-ray is erosion, which is associated with progressive joint destruction in the late phase of RA, especially in patients not receiving appropriate therapy [1]. Positive autoantibodies such as anti-cyclic citrullinated peptide antibody (ACPA), rheumatoid factor (RF), and high disease activity are additional predisposing factors for joint destruction, indicating that autoimmune-mediated inflammation is implicated in joint damage in both cartilage and bone [2–5]. Specifically, in the “treat-to-target” concept, management of RA primarily aims to induce early clinical remission and, subsequently, maintain responses that are mainly focused on suppressing inflammation [6]. Prompt treatment reduces inflammation, resulting in limited structural change and better long-term radiologic outcomes [7]. However, according to subjective symptoms, objective signs, and laboratory data, joint lesions can progress latently even in clinical remission. As supportive imaging techniques, magnetic resonance imaging (MRI) and ultrasonography (US) are recommended to be applied for making the diagnosis, monitoring the disease activity, and detecting subclinical inflammation even in patients in clinical remission [8]. For example, we and other groups have reported US-detected synovitis with power Doppler (PD) signal associated with joint destruction, even in RA patients with clinical remission [9].

Recently, advances in the field of osteoimmunology have resulted from investigating RA and analyzing cellular and molecular interactions between the immune system and bone tissue [10,11]. Longitudinal observations of the clinical course of RA patients have indirectly implicated the inflammatory process in bone destruction [7]. However, few studies have simultaneously evaluated joint inflammation and bone metabolism in patients with RA.

Positron emission tomography/computed tomography (PET/CT) has established the anatomicomolecular imaging modality combined functional and structural evaluation. In this study, we used two tracers: 18F-fluorodeoxyglucose (FDG) and 18F-fluoride (NaF). 18F-FDG, a glucose analog, is the most common tracer; it is taken in by metabolically active cells, such as neoplastic cells.
According to recent studies, 18F-FDG PET sensitively detects active inflammation in rheumatic diseases, including synovitis in RA [12–18]. In contrast, 18F-NaF PET is an increasingly used molecular imaging modality in human skeletal disorders [19–23]. 18F-NaF incorporates into the bone at the site of bone formation or remodeling; there, osteoblasts and osteoclasts are activated, and 18F ions exchange the hydroxyl ions in bone crystal to form fluorapatite. In addition to bone metabolism, the rate-limiting step of 18F-NaF bone uptake is blood flow [24]. 18F-NaF PET is useful for monitoring pathologic changes in the bones of experimental arthritis [25] and illustrating osteoplastic lesions in human joint diseases, such as osteoarthritis (OA) [21] and psoriatic arthritis [22].

Here, we compared 18F-FDG and 18F-NaF PET/CT analyses of the hands with other imaging modalities and clinical assessment in RA patients requiring biologic disease-modifying antirheumatic drugs (bDMARDs) for active disease. Moreover, we investigated the relationship of these PET findings with radiologic progression of the joint lesions.

Patients and methods

Patients

We enrolled 12 patients (10 female, 2 male; average age, 60.0 ± 15.9 years) at Yokohama City University Hospital who fulfilled the American College of Rheumatology 1987 classification criteria for RA [26]. Nine patients started the first bDMARD (etanercept 4, infliximab 2, golimumab 1, and tocilizumab 2), whereas 3 patients switched from infliximab to golimumab, tocilizumab, or abatacept. The study was approved by the ethics committee of our institute, and all patients gave their written informed consent. Multimodality imaging assessments, including X-ray, 18F-FDG and 18F-NaF PET/CT, of bilateral hands and wrists were completed within 4 days prior to starting or switching bDMARDs. In addition, MRI was performed in all patients except one, who had a permanent pacemaker. For 6 months after the first imaging assessment, we monitored swollen joint counts, tender joint counts, patient’s and physician’s global assessments, patient’s pain assessments, and modified health assessment questionnaires (MHAQs) [27]. Using the erythrocyte sedimentation rate (ESR), we calculated the disease activity score in 28 joints (DAS28) according to the established formula [28]. To assess bone turnover, we measured serum osteocalcin, serum bone alkaline phosphatase, and total urinary deoxypyridinoline levels at baseline.

Hand X-ray

Radiographs of joints in the hands and wrists were assessed at baseline and 6 months according to the Genant-modified Sharp scoring system [29] by three independent readers blinded to the treatment assignment, clinical findings, and chronologic order of radiographs. The inter-reader agreement was acceptable (κ = 0.78). Total radiographic score was composed of erosion score plus joint space narrowing (JSN) score. Each site was evaluated in 0.5-unit increments. Erosion scores of 0–3.5 are assigned to 14 sites in each hand and wrist. JSN scores of 0–4 are assigned to 13 sites in each hand.

PET scanning

18F-FDG and 18F-NaF PET/CT scans were performed using a SET 2400 W (Shimadzu, Kyoto, Japan). Blood glucose levels were lower than 150 mg/dL after fasting more than 6 h when 2.5 MBq/kg of 18F-FDG was injected into the patients. After 60 min of an uptake phase, data of PET in the bilateral hands were acquired for 2 min in prone with arm up position. More than 24 h later 18F-NaF PET scan was conducted for 2 min scanning of the hands after injection with 185 MBq of the tracer followed by 40 min of uptake. A multislice helical non-contrast CT scan was obtained prior to each PET scanning and used for attenuation correction and anatomic information of the PET images. The spatial resolution of the PET was 2.5 mm pixel size in this study. Experienced radiologists determined hypermetabolic areas in bilateral metacarpophalangeal (MCP), proximal interphalangeal (PIP), and wrist (radiocarpal, ulnocarpal, and intercarpal) joints. The maximum standardized uptake value (SUVmax) in individual joints was determined according to the following equation:

\[ \text{SUVmax} = \text{maximal count} \times \text{calibration factor (kBq/mL)/ injected activity (MBq/body weight (kg))}. \]

The SUVmax in the wrist joint was determined by the highest SUVmax among those of the radiocarpal, ulnocarpal, and intercarpal joint regions. The sum of the SUVmax for all 26 joint regions was calculated.

MRI

As an option, we performed MRI mainly as a reference to other imaging modalities. Plain MRIs of the wrist and fingers were acquired using a 1.5-Tesla scanner (Gyrosan Intera Master, Philips Medical Systems, Eindhoven, Netherlands), according to the institute’s routine procedure at study of the entry. The imaging protocol comprised a coronal short T1 inversion recovery sequence (repetition time, 4,000–4,200 ms; echo time, 80 ms), followed by coronal and axial T1-weighted spin echo images (repetition time, 500–600 ms; echo time, 11 ms). The slice thickness was 3 mm.

Statistical analysis

Correlations were investigated using Spearman’s rank correlation. Chi-square and unpaired t-tests were used to compare radiopharmaceutical uptake in the joints with and without progressive erosions. P values less than 0.05 were considered statistically significant. A stepwise multivariate regression analysis was conducted to test the independent determinants of the estimated yearly radiographic progression. The independent variables included tender joint count, swollen joint count, patient’s global assessment, physician’s global assessment, DAS28-ESR, MHAQ, C-reactive protein (CRP), ESR, matrix metalloproteinase-3 (MMP-3), osteocalcin, bone alkaline phosphatase, urinary deoxypyridinoline, sum of the SUVmax of 18F-FDG, and sum of the SUVmax of 18F-NaF. All statistical analyses were performed in SPSS version 11.0 (IBM Japan, Tokyo, Japan).

Results

Demographics and baseline characteristics

Table 1 summarizes the baseline clinical profiles of the patients in this study. All patients were positive for ACPA. The disease duration was from 3 months to 22 years. No patients had achieved clinical remission (based on DAS28) at entry, despite previous treatment with low-dose prednisolone (4–15 mg/day) in 6 patients, methotrexate (6–16 mg/week) in 9 patients, and infliximab in 3 patients. Radiologic bone erosions in any joint were found in 10 of 12 patients (83.3%). After the first set of multimodality imaging analyses, 9 patients began receiving bDMARDs and 3 patients were switched from infliximab to other bDMARDs. Of them, the standard therapeutic protocols of individual biologic agents were completed in 6 of 12 patients. Otherwise, the biologic agents were discontinued within 6 months of observation period in 4 patients including 3 due to complicated infection and one due to surgical operation. The dose of tocilizumab was modified in a patient, whereas lupus-like manifestations developed in a patient receiving infliximab at 6 months.
First, we analyzed the $^{18}$F-NaF and $^{18}$F-FDG PET/CT images at entry. In a 74-year-old male with a 13-year history of RA (Figure 1A), both tracers accumulated in the 2nd MCP joint, which had swelling and tenderness and bone erosion in the metacarpal bone head on the plain radiograph. $^{18}$F-NaF signals were located on the bone cortex, whereas $^{18}$F-FDG signals were mainly in the joint space adjacent to the bone. Thus, upregulated bone turnover is likely associated with active inflammation. In contrast, $^{18}$F-NaF accumulated not only in joints with erosion but also in the 3rd distal interphalangeal (DIP) joint. According to radiography, osteophyte as well as JSN and subchondral sclerosis was observed in this joint, which was considered to be an OA change (Figure 1B).

We compared the uptake of both tracers in 26 joint regions, including all PIP and MCP joints and radial, medial, and ulnar regions of the wrists. $^{18}$F-FDG and $^{18}$F-NaF accumulated in 73% of joint regions.

Table 1. Baseline characteristics of patients.

| Variables                        | Total (n = 12) |
|----------------------------------|---------------|
| Gender Female (%)                | 10 (83.3%)    |
| Age (Years (mean ± SD))          | 60.0 ± 15.9   |
| Disease duration (Years (mean ± SD)) | 6.8 ± 7.3   |
| BMI (kg/m² (mean ± SD))          | 21.2 ± 3.5    |
| Experience of smoking n (%)      | 4 (33.3%)     |
| Swollen joint count, (28 joints) n (mean ± SD) | 6.4 ± 5.5   |
| Tender joint count, (28 joints) n (mean ± SD) | 6.2 ± 5.6   |
| DAS28-ESR (mean ± SD)            | 4.8 ± 1.4     |
| MHAQ (mean ± SD)                 | 0.7 ± 0.5     |
| CRP (mg/dl (mean ± SD))          | 2.0 ± 2.6     |
| ESR (mm/hr (mean ± SD))          | 33.8 ± 21.4   |
| MMP-3 (ng/ml (mean ± SD))        | 158.9 ± 108.4 |
| ACPA positive n (%)              | 12 (100%)     |
| RF-IgM positive n (%)            | 9 (75.0%)     |
| Concomitant medications Corticosteroid n (%) | 6 (50.0%)     |
| Methotrexate n (%)               | 9 (75.0%)     |
| Radiographic scores Total radiographic score (mean ± SD) | 17.1 ± 19.0 |
| Bone erosion score (mean ± SD)   | 5.0 ± 7.9     |
| Joint space narrowing score (mean ± SD) | 12.1 ± 11.5 |
| PET Sum of the SUVmax of $^{18}$F-FDG (mean ± SD) | 20.3 ± 15.4 |
| Sum of the SUVmax of $^{18}$F-NaF (mean ± SD) | 62.1 ± 35.3 |

$^{18}$F-FDG and $^{18}$F-NaF uptake in individual joints

We compared the uptake of both tracers in 26 joint regions, including all PIP and MCP joints and radial, medial, and ulnar regions of the wrists. $^{18}$F-FDG and $^{18}$F-NaF accumulated in 73% of joint regions.

Figure 1. Anatomical localization of $^{18}$F-FDG and $^{18}$F-NaF PET signals.

(A) A 74-year-old male with a 13-year history of RA. Bone erosion was found in the 2nd metacarpal bone head in plain X-ray. $^{18}$F-NaF signals were located on the bone cortex, while $^{18}$F-FDG signals were observed in the joint space. (B) A 68-year-old female with a 3-month history of RA. $^{18}$F-NaF accumulated not only in joints with erosion but also in the 3rd DIP joint. According to radiography, osteophyte as well as JSN and subchondral sclerosis was observed in this joint, which was considered to be an OA change.
and 82% of swollen joints and 16% and 30% of non-swollen joints, respectively. The SUVmax values of $^{18}$F-FDG and $^{18}$F-NaF were significantly correlated in individual joints (Figure 2A); however, there was a discrepancy in accumulation in some joints.

We separately analyzed radiographic OA change-positive ($n = 47$) and -negative ($n = 265$) joints in RA-prevalent joint regions (Figure 2B). There was a significant correlation between the SUVmax of the two tracers, irrespective of the presence or absence of OA change.

$^{18}$F-FDG and $^{18}$F-NaF PET uptake and clinical assessments at baseline

$^{18}$F-FDG and $^{18}$F-NaF peak uptake parameters, which were calculated by summation of the SUVmax in 26 joint regions, were 20.3 ± 15.4 and 62.1 ± 35.3, respectively. The sum of the SUVmax of $^{18}$F-NaF; but not $^{18}$F-FDG, correlated with clinical disease activity, according to DAS28 and physical function assessed by MHAQ at baseline (Supplementary Table 1 to be found online at http://informahealthcare.com/doi/abs/10.3109/14397595.2015.1069458). In addition, the sum of the SUVmax of $^{18}$F-NaF correlated with MMP-3, but neither score correlated with other laboratory parameters.

$^{18}$F-FDG and $^{18}$F-NaF PET/CT and bone erosion in X-rays

Baseline X-rays revealed erosive lesions in 44 of 312 joints in the 12 RA patients. SUVmax of $^{18}$F-NaF and $^{18}$F-FDG were significantly higher in erosive joints than non-erosive joints ($^{18}$F-NaF erosive 7.32 ± 6.89 vs. non-erosive 1.58 ± 2.48, $p < 0.001$; $^{18}$F-FDG erosive 1.55 ± 1.65 vs. non-erosive 0.65 ± 1.12, $p < 0.001$).

All patients underwent the follow-up X-ray imaging of the hands at 6 months. The estimated yearly progression of total radiographic scores significantly correlated with the sum of the SUVmax of $^{18}$F-NaF ($r = 0.69, p = 0.014$) but not $^{18}$F-FDG ($r = 0.05, p = 0.879$) (Supplementary Table 2 to be found online at http://informahealthcare.com/doi/abs/10.3109/14397595.2015.1069458), and was elevated by more than 0.5 points in 10 patients, unchanged in another, and reduced in one. Sum of the SUVmax of $^{18}$F-NaF was significantly correlated with the progression of bone erosion ($r = 0.58, p = 0.045$) but not with JSN ($r = 0.47, p = 0.12$) in two components of the total radiographic score.

A stepwise multivariate regression analysis was carried out to test the independent determinants of radiographic progression. We found that the SUVmax of $^{18}$F-NaF ($\beta = 0.66, p = 0.028$) were the only variables independently associated with radiographic progression among clinical backgrounds, physical findings, disease activity, laboratory data including bone metabolism markers, and PET findings (Table 2).

We then analyzed $^{18}$F-NaF and $^{18}$F-FDG PET in individual joints, which were divided into subgroups according to interval change for the 6-month observation. Erosive joints ($n = 44$) at the baseline were divided into persistent ($n = 12$), progressive ($n = 22$), and repaired ($n = 10$) groups; other groups were non-erosive joints ($n = 268$) including unchanged joints ($n = 246$), and newly developed erosion ($n = 22$) (Figure 3A). SUVmax for $^{18}$F-NaF was the highest in the progressive erosion group, followed by the persistent erosion group; SUVmax for $^{18}$F-FDG was also significantly higher in the progressive erosion group than in the other groups except the repaired group (Figure 3B). Accumulation of both tracers in a particular joint was divided into 4 patterns: $^{18}$F-NaF+/$^{18}$F-FDG+, $^{18}$F-NaF+/$^{18}$F-FDG-, $^{18}$F-NaF-/ $^{18}$F-FDG+, and $^{18}$F-NaF-/ $^{18}$F-FDG-. The $^{18}$F-NaF+/ $^{18}$F-FDG+ pattern was significantly more frequent in the progressive erosion joints than in any other subgroup; however, $^{18}$F-NaF-/ $^{18}$F-FDG- was the most dominant pattern in the non-erosive joints (Figure 3A). Therefore, bone lesion progression was likely associated with the uptake of both tracers in the joints.

Comparison with interval changes of MRI

We conducted follow-up $^{18}$F-FDG and $^{18}$F-NaF PET/CT and MRI at 6 or 12 months in 2 patients (Figure 4). In Case 3 (Figure 4A), golimumab was initiated at study entry because of high disease activity (DAS28 5.69) had been persistent. The patient showed a moderate response to golimumab (DAS28 4.72), but clinical efficacy was not apparent in the left wrist, in which tenderness and swelling remained at 6 months. The baseline $^{18}$F-FDG accumulated mainly in the ulnocapitate and radioscaphoid joint spaces; however, diffuse $^{18}$F-NaF uptake was found in the carpal bones but not the radius or ulna. These signals remained in the follow-up PET examinations at 6 months, and the MRI detected a newly developed erosion in the lunate bone.

In contrast, Case 4 (Figure 4B) achieved clinical remission (DAS28 2.91 at baseline to 1.42 at 6 months) with etanercept and maintained remission at 12 months. The right wrist joints also showed clinical improvement. $^{18}$F-NaF uptake was diffuse throughout the carpal bones of the left wrist joint, whereas weak $^{18}$F-FDG accumulation was present in the joint spaces at baseline. At the 12-month follow-up examination, $^{18}$F-FDG signals were almost undetectable; however, significant $^{18}$F-NaF signals remained in two regions: the carpal articular surface of the radius and the joint surface of the capitae. In accordance with the remaining $^{18}$F-NaF signals, erosions were repaired. Therefore, $^{18}$F-NaF accumulation without $^{18}$F-FDG signals can be detected in bone undergoing repair.

Discussion

In the present study, $^{18}$F-FDG and $^{18}$F-NaF PET/CT illustrated the affected joints of RA patients; overall accumulation of $^{18}$F-NaF correlated with clinical assessment and physical disability. According to comparative analysis with radiographic images,
18F-NaF accumulation was associated with the presence of erosive lesions and ongoing bone damage; 18F-FDG uptake also reflected this damage. In contrast, 18F-NaF and 18F-FDG signals were not detected in most of the intact joints. The concordant distribution of both tracers in the same joints suggests coupling of inflammation with upregulated bone turnover in RA-affected joint lesions. Although the patterns of 18F-NaF and 18F-FDG accumulation did not exactly overlap, the inflammation and bone turnover reveal both lead to bone destruction.

A number of 18F-FDG PET studies have shown that 18F-FDG is incorporated into the inflammatory cells of soft tissues, including macrophages, capillaries, and fibroblasts; osteoclasts also take up the tracer in bone [30], and that the accumulation in RA-affected joint lesions correlates with disease activity [14–18]. 18F-NaF is directly incorporated into the areas of bone with upregulated turnover; however, blood flow is a rate-limiting step of the tracer’s uptake [24], indicating that this imaging technique has potential to reflect two main pathologic components: hypervascularity and bone destruction in RA. Furthermore, in experimental animal arthritis, 18F-NaF PET shows a correlation between the tracer accumulation and progression of bone destruction [25]. Irmler IM et al. reported the relationship of 18F-FDG and 18F-NaF uptakes and joint destruction [25,31]. 18F-FDG uptakes, which correlated with arthritis score, start to increase at Day 9 and reach the peak at Day 11 followed by decline. On the other hand, 18F-NaF signals, which correlated with bone destruction, were elevated and sustained after Day 11. The maximum incorporation was noted from Day18 to 25, when arthritis has already subsided. Thus, the data suggest that inflammation is followed by bone destruction.

Table 2. Stepwise multiple linear regression analysis for the effect of independent variable on radiographic progression.

| Variable | β-coefficient | 95% CI | p value |
|----------|---------------|--------|---------|
| Sum of the SUVmax of 18F-NaF | 0.66 | 0.02–0.31 | 0.028 |

R-square = 0.43.

18F-NaF PET/CT findings and radiological changes of bone lesions. 18F-FDG and 18F-NaF PET/CT findings were compared among 5 groups, which were divided according to radiological findings at the baseline and interval changes for 6 months. (A) Signal intensities of 18F-FDG and 18F-NaF were significantly higher in erosive joints than non-erosive ones, and were the highest in joints having erosion with further progression. (B) In analysis of accumulation patterns of 18F-FDG and 18F-NaF, simultaneous accumulation of the both tracers was significantly more frequent in joints having erosion with further progression than any other groups.

Figure 3. 18F-FDG and 18F-NaF PET/CT findings and radiological changes of bone lesions. 18F-FDG and 18F-NaF PET/CT findings were compared among 5 groups, which were divided according to radiological findings at the baseline and interval changes for 6 months. (A) Signal intensities of 18F-FDG and 18F-NaF were significantly higher in erosive joints than non-erosive ones, and were the highest in joints having erosion with further progression. (B) In analysis of accumulation patterns of 18F-FDG and 18F-NaF, simultaneous accumulation of the both tracers was significantly more frequent in joints having erosion with further progression than any other groups.
Figure 4. Interval changes in $^{18}$F-FDG and $^{18}$F-NaF PET and MRI findings of the wrist: representative cases.

(A) A 71-year-old female with a 6-year history of RA. The baseline examinations showed accumulation of $^{18}$F-FDG in ulnocapitate and radioscaphoid joint spaces and that of $^{18}$F-NaF diffusely. These signals remained in the follow-up PET examinations at 6 months, whereas MRI detected newly developed erosion in the lunate bone.

(B) A 68-year-old female with a 6-month history of RA. The baseline examinations showed diffuse uptake of $^{18}$F-NaF and weak accumulation of $^{18}$F-FDG in the joint spaces in the left wrist joint. The signals disappeared except two $^{18}$F-NaF incorporated regions with repairing erosion shown by MRI.

No $^{18}$F-NaF signal was detected until clinical findings of the joint lesions appeared; therefore, autoimmune inflammation is followed by bone lesions [25].

Bone scintigraphy using 99mTc-labeled bisphosphonate has been used as a nuclear imaging technique to detect joint inflammation in RA until $^{18}$F-NaF PET is available [32]. Accumulation of 99mTc bisphosphonate, which is found in periarticular bone lesions with osteolytic lesion and hypervascularity, predicts later erosion [33]. Specificity to detect bone lesions is greatly improved by introduction of SPECT/CT, but further significantly improved with use of $^{18}$F-NaF PET/CT [23,34].

In concordance with previous reports, $^{18}$F-NaF was preferentially incorporated into erosive lesions in our study; the highest signals were associated with progressive erosion [24]. Furthermore, the overall accumulation correlated with progression of erosion (Supplementary Figure 1 to be found online at http://informahealthcare.com/doi/abs/10.3109/14397595.2015.1069458. Numerous studies show that total US-PD signals are associated with bone destruction, especially in cases of longer lasting, more active inflammation [35–37]. However, $^{18}$F-NaF PET more directly detects ongoing bone destruction in RA-affected joints compared with other imaging modalities.

We compared findings in individual joints of hands between $^{18}$F-NaF and $^{18}$F-FDG PET/CT scans. There is a close correlation between $^{18}$F-FDG and $^{18}$F-NaF accumulations in the joints of RA patients irrespective of OA changes. However, typical OA lesions (Figure 1B, in DIP joints) incorporated $^{18}$F-NaF but not $^{18}$F-FDG, though DIP joints were not systematically assessed in this study. Moreover, according to previous reports, some OA lesions take up $^{18}$F-FDG [34,38]; therefore, secondary synovitis is likely accompanied by OA. Alternatively, RA synovitis may be complicated osteoplastic changes in our patients, because the observation was restricted to RA-prevalent joints.

Combining PET with CT scanning is helpful for identifying anatomical localization of PET signals. The anatomic distributions of the markers in some joints differed between $^{18}$F-NaF and $^{18}$F-FDG (Figure 1A). Specifically, $^{18}$F-NaF accumulated in erosive lesions of the bone cortex; $^{18}$F-FDG signal was located in the surrounding
soft tissues. These differential distributions are reasonable considering the pharmacologic features of the tracers. However, the spatial resolution of PET/CT was insufficient to identify detailed localization in many cases, especially when the signals are too intense [39]. The issue is one of the major limitations of PET/CT in small joint analysis. Recent pilot studies have shown that spatial resolution of PET image in hand small joints is improved by use of dedicated PET imaging devices [34], or high-resolution PET with MRI scanner [40].

The present study has several limitations due to the study design and nature of $^{18}$F-NaF as a tracer. We enrolled RA patients that required the first or second bDMARD with a wide range of disease duration; however, the sample size was too small to discuss the effects of various background factors (such as disease stage and therapies) on findings of PET findings.

$^{18}$F-NaF is incorporated into not only RA-associated bone destructive lesions but also osteopoetic lesions caused by other disorders, such as OA. Moreover, strong $^{18}$F-NaF signals were found in areas of bone erosion repair in a patient with a favorable clinical response to etanercept (Figure 4B, Case 4). Case 4 showed that remaining $^{18}$F-NaF signals reflected undergoing repair. This is compatible with the finding that $^{18}$F-NaF signals last longer than the $^{18}$F-FDG signals after subsiding arthritis in experimental animal models. Erosive progression occurred simultaneously with repair in other joints in the same patients, as we previously reported [41]. Therefore, it is difficult to determine the pathology on the basis of the finding of $^{18}$F-NaF PET alone. Rather, comprehensive assessment together with other modalities is essential to characterize the pathology of $^{18}$F-NaF-positive sites. Another concern is radiation exposure in clinical application; repeated examinations are not recommended because computed tomography dose index volume is estimated as 9.9 mGy per test. The radiation dose for a whole-body study is 25 mGy.

In summary, co-existing PET signals of $^{18}$F-NaF and $^{18}$F-FDG in the affected joints suggest that inflammation is coupled with upregulated bone turnover, leading to joint destruction. In particular, joints with strong signals of both tracers are likely to have progressive bone destruction in the near future.

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Conflict of interest

None.

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Supplementary material available online
Supplementary Tables 1, 2 and Figure 1 to be found online at http://informahealthcare.com/doi/abs/10.3109/14397595.2015.1069458