^{18}F-FDG positron emission tomography as a marker of disease activity and treatment response in Ankylosing Spondylitis and Psoriatic Arthritis

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Abstract

Objectives

The ability of ^{18}F-FDG positron emission tomography (PET) to track disease activity and treatment response in patients with Ankylosing Spondylitis (AS) or Psoriatic Arthritis (PsA) remains unclear. Here, we assessed whether ^{18}F-FDG uptake is a marker of disease activity and treatment response in AS or PsA, and explored the ability of ^{18}F-FDG to predict treatment response.

Methods

Patients with AS (n = 16) or PsA (n = 8) who were scheduled to initiate treatment with biologics were recruited. Participants underwent a clinical evaluation and an ^{18}F-FDG scan prior to therapy initiation. Eleven participants underwent a follow-up ^{18}F-FDG scan 3 months post-treatment. Images were quantified using a composite measure that describes the inflammatory status of the patient.

Results

Clinically involved joints/entheses had higher ^{18}F-FDG uptake compared to unaffected areas (median difference > 0.6, $p < 0.01$). Among patients with AS, pre-treatment ^{18}F-FDG uptake was strongly associated with disease activity (r = 0.65, $p = 0.006$). Longitudinal ^{18}F-FDG scans demonstrated that decreases in uptake at 3 months were associated to clinical response ($\beta_{\Delta gSUVmax} > 8.5$, $p < 0.001$). We found no significant association between pre-treatment ^{18}F-FDG uptake and subsequent clinical response.

Conclusions

^{18}F-FDG PET shows potential as a marker of disease activity in AS and PsA, allowing for monitorization of biological treatment efficacy in these patients.

Introduction

Seronegative spondyloarthropathies (SpA) represent a heterogeneous group of chronic inflammatory disorders characterized by axial or peripheral arthritis and enthesitis, typically accompanied by extra-articular features such as uveitis, psoriasis, and inflammatory bowel disease (1). SpA includes ankylosing spondylitis (AS), psoriatic arthritis (PsA), reactive arthritis, inflammatory bowel disease-related arthritis, and undifferentiated SpA. Among these, AS and PsA are the two most prevalent phenotypes, contributing to approximately 60–80% of all SpA cases (2).

One of the fundamental pathological signatures of SpA are inflammation of the entheses and synovial tissue, though ligaments and bone marrow can also be affected (3, 4). These inflammatory processes are closely associated with the severity of clinical symptoms and disease activity (5, 6), thus accurate and

objective assessment of inflammation is crucial for early diagnosis and monitoring therapeutic response in patients with SpA.

To date, standard radiography and magnetic resonance imaging (MRI) are key imaging modalities for the diagnosis and management of patients with SpA (7–9). While X-rays can only describe established damages occurring at later stages (8), MRI is more sensitive to earlier inflammatory processes such as bone marrow edema (10) and is therefore considered the gold standard modality for the assessment of early pathological changes in SpA (9). MRI can also detect structural damage such as fat lesions, erosion, sclerosis, and ankylosis (11–13). Yet, despite these valuable diagnostic features, MRI has shown to be a poor marker of disease activity in previous randomized controlled trials and longitudinal studies (9, 14, 15), and thus there is a need for more accurate markers of disease activity that can substantially improve monitorization of disease progression in clinical trials and practice.

The ability of positron emission tomography (PET) imaging to detect inflammatory changes at the molecular level before structural changes occur suggests that PET may overcome the current limitations of MRI. PET imaging can accurately reflect the pathological signatures of SpA, specifically inflammation —with tracers such as ^{18}F-FDG PET (16–18)—and osteoblastic activity—with e.g. ^{18}F-sodium fluoride (NaF) PET (19, 20). Findings from prior cross-sectional studies demonstrated that PET with ^{18}F-FDG or ^{18}F-NaF depicts active lesions in AS (16, 20, 21), PsA (22, 23), and other seronegative arthritis (24). However, conflicting findings on the diagnostic performance of PET with ^{18}F-FDG or NaF have been reported (25, 26), and the field still lacks key studies confirming the utility of PET for the clinical assessment of SpA or for treatment trials.

In the present study, we contribute to fill the current knowledge gap in SpA diagnostics by performing an analysis of the ability of ^{18}F-FDG PET to monitor disease progression in patients with AS or PsA who are scheduled to initiate biological treatment (27). For this, we provide novel data investigating how cross-sectional ^{18}F-FDG PET signal intensity associates with the severity of clinical symptoms in AS and PsA patients. Furthermore, we performed longitudinal ^{18}F-FDG PET scans to assess whether PET signal changes over time do actually reflect clinical improvements related to therapy. Finally, we explored the ability of ^{18}F-FDG PET in predicting treatment response.

Materials and Methods

Participants and study design

We prospectively included patients with a prior diagnosis of AS (n = 16) or PsA (n = 8) who were referred to the Rheumatology unit at the Central University Hospital of Asturias to initiate biological treatment (anti-TNF or anti-Il17 inhibitors). Eligible patients must be ≥ 18 years of age, have a life expectancy of more than 12 months, and be willing and able to undergo testing procedures, including musculoskeletal imaging. Participants must not have been treated with biologics before, must meet criteria for prior treatment failure with non-steroidal anti-inflammatory (NSAIDs) or disease-modifying antirheumatic

drugs (DMARDs) (27), and must not have contraindications to biological therapy. Exclusion criteria include pregnancy/breast-feeding, current treatment with immunosuppressants, other comorbid inflammatory joint disease, presence of clinically significant opportunistic infections, a cancer diagnosis in the past 5 years, history of bleeding diathesis or inherited coagulation disorders, diabetes mellitus with poor glycemic control (>150), major surgery in the past three months, and have had a non-study related investigational treatment procedure within 28 days prior to screening.

All participants underwent a comprehensive clinical evaluation one week before the scheduled initiation of biological treatment—baseline visit—, as well as at 3- and 6-months post-baseline (except for 1 AS and 1 PsA participants who did not complete the 6-month visit). All participants underwent ^{18}F-FDG PET at baseline, and 6 AS and 5 PsA participants also underwent a longitudinal ^{18}F-FDG PET scan at 3 months post-baseline.

The study protocol was approved by the Central University Hospital of Asturias' Ethics and Clinical Research Committee. All patients provided written informed consent prior to participation in the study. This study was performed in accordance with the Declaration of Helsinki.

Clinical assessments

Clinical evaluations were performed by a certified rheumatologist at the Rheumatology unit of the HUCA. For AS participants, disease activity was assessed using the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) (28). For PsA participants, disease activity was monitored with the Disease Activity Index for Psoriatic Arthritis (DAPSA) (29).

^{18} F-FDG PET acquisition

Whole-body ^{18}F-FDG PET/CT scans were acquired as per standard institutional protocol at the Nuclear Medicine department of HUCA on a GE Discovery 710 PET/CT scanner. Patients fasted for at least 6 hours prior to the injection of 0.1 mCi/Kg of ^{18}F-FDG. Scans were acquired 50 to 60 minutes post-injection using a scanning time of 2.5 minutes per bed position. Three-dimensional PET images were reconstructed using the ordered subset expectation maximization algorithm (3 iterations, 18 subsets) accounting for time-of-flight. Low-dose CT (50–300 mA, 120 kV) was performed previous to the PET acquisition for attenuation correction and localization of PET signal and was not used for identification of structural bone lesions.

Image analysis

An experienced Nuclear Medicine physician (OR-F), blinded to clinical information, analysed the acquired ^{18}F-FDG PET images in a semiquantitative manner. Seventeen peripheral joints (shoulders, elbows, carpal-metacarpophalangeal, hips, knees, tarsal-metatarsophalangeal, spine, and sacroiliac) and 18 entheses (costochondral joints, L5 spinous process, anterior superior iliac spine, iliac crest, posterior iliac spine, pubic symphysis, ischial tuberosities, tibial tuberosities, and Achilles tendons) were evaluated. For

each joint/enthesis, a two-dimensional region of interest (ROI) was manually drawn, and the maximum standardized uptake value (SUV_{max}) within the ROI was measured.

To globally describe the inflammatory status of the patient, we defined a composite index based on the SUV_{max} measured on the clinically affected joints/entheses at baseline. For this, we first averaged the SUV_{max} measured on the spine, hips, and knee joints with the SUV_{max} measured on their corresponding entheses (L5, greater trochanter, and patellar tendons, respectively), as it was challenging to reliably determine whether there was joint or entheseal involvement in these regions. Then, we derived a global SUV_{max} ($gSUV_{max}$) index by averaging the SUV_{max} (with the aforementioned modification) of the clinically affected regions at baseline. Note that, for longitudinal ^{18}F-FDG PET scans, $gSUV_{max}$ is derived using the longitudinal SUV_{max} measured on the clinically involved regions at baseline.

Statistical Analysis

Sign tests were used to compare the medians of the distributions of average SUV_{max} in clinically uninvolved vs clinically involved regions, as well as to compare the medians of the distributions of baseline $gSUV_{max}$ vs post-baseline $gSUV_{max}$. Cross-sectional relationships between $gSUV_{max}$ and baseline disease activity (BASDAI or DAPSA) were assessed using linear regression and the corresponding correlation coefficient (r). The association between $gSUV_{max}$ change at 3 months ($\Delta gSUV_{max} = gSUV_{max,3m} - gSUV_{max,bl}$) with change in disease activity at 3- and 6-months follow-up was assessed using linear mixed effects (LME) models. The LME model included change from baseline in the respective disease activity score (BASDAI or DAPSA) as dependent variable. Model's fixed effects included a study visit term (categorical variable, 3- and 6-months), baseline score, and $\Delta gSUV_{max}$, as well as visit-by-baseline score and visit-by-$\Delta gSUV_{max}$ interactions. A subject-specific intercept was included as random effects. Identical models were run for the analysis of the association between baseline $gSUV_{max}$ and disease activity change, replacing $\Delta gSUV_{max}$ by baseline $gSUV_{max}$.

Results

Baseline and follow-up cohort characteristics

Demographics and baseline clinical characteristics of the study participants are summarized in Table 1. Overall, AS and PsA participants had similar age and disease duration distributions. The distribution of previous, non-biologic treatments was similar across AS and PsA patients, except for disease-modifying therapies, which were more commonly used in PsA patients. AS participants had more entheseal involvement, while PsA participants had more painful/swollen/tender joints. Both AS and PsA participants had moderate/high disease activity (BASDAI>4 and DAPSA>18). After the baseline clinical evaluation, 2 PsA patients did not initiate treatment with biologics as per indication of their managing rheumatologist.

Table 1. Characteristics of the study participants.

	Ankylosing Spondylitis (n=16)	Psoriatic Arthritis (n=8)
Males/Females	7/9	4/4
Age, median years (IQR)	39 (16)	48 (16)
HLA-B27-positive, %	15 (94)	NA
Duration since diagnosis, median years (IQR)	6.7 (9.7)	5.0 (15.0)
Previous non-biologic treatments		
• NSAIDs, n (%) • Oral corticosteroid, n (%) • Non-NSAIDs analgesic, n (%) • DMARDS, n (%)	16 (100) 3 (18) 2 (12) 2 (12)	8 (100) 2 (25) 3 (38) 6 (75)
Scheduled biologic treatment at baseline		
• Adalimumab, n (%) • Golimumab, n (%) • Etanercept, n (%) • Secukinumab, n (%) • Did not begin biologic treatment, n (%)	13 (81) 2 (12) 1 (6) 0 0	5 (62) 0 0 1 (12) 2 (25)
Number of painful/swollen/tender joints, average (range)	4 (1-12)	7 (4-11)
Number of painful/swollen/tender entheses, average (range)	2 (0-11)	1 (0-3)
Baseline BASDAI, median (range)	4.5 (4-5.5)	NA
Baseline DAPSA, median (range)	NA	27.0 (9.0)
3-month BASDAI adjusted mean change from baseline, mean (95% CI)	-1.3 (-1.8 to -0.8)	NA
3-month DAPSA adjusted mean change from baseline, mean (95% CI)	NA	-8.8 (-17.5 to -0.03)
6-month BASDAI adjusted mean change from baseline, mean (95% CI)	-1.8 (-2.3 to -1.3)	NA
6-month DAPSA adjusted mean change from baseline, mean (95% CI)	NA	-11.8 (-20.5 to -3.0)

At the 3-month follow-up visit, 2 AS participants changed their biologic treatment due to lack of efficacy (Adalimumab); the remaining participants continued with their prescribed biologic at baseline, and the 2 PsA participants that did not initiate treatment at baseline continued without biologic therapy. Both AS

and PsA participants undergoing biologic therapy showed statistically significant improvements in their clinical symptoms at both 3- and 6-month follow-up (Table 1, last 4 rows).

Cross-sectional associations

First, we investigated whether active disease associated with changes in ^{18}F-FDG uptake. Clinically involved—painful/swollen/tender—joints and/or entheses had significantly higher average SUV_{max} ($gSUV_{max}$) compared to the average SUV_{max} of pain- and inflammation-free joints/entheses (Figures 1A, 1B, 1C, AS: median SUV difference = 0.61, p<0.001; PsA: median SUV difference = 0.72, p=0.008). Furthermore, we found that baseline $gSUV_{max}$ was strongly associated with baseline disease activity in AS (r=0.65, p=0.006, Figure 1D); no statistically significant association was found for PsA participants (r=-0.37, p=0.37) (Figure 1E).

Longitudinal associations

Next, we analysed the longitudinal changes in ^{18}F-FDG uptake at 3-months and its relationship with changes in disease activity at 3- and 6-months after the initiation of biologic therapy. We found that $gSUV_{max}$ decreased in both AS (median change = -0.41) and PsA (median change = -0.26) participants at 3-months follow-up, though these changes reached statistical significance only in AS patients (Figure 2A-C). In addition, more pronounced $gSUV_{max}$ decreases (i.e. more negative $\Delta gSUV_{max}$) at 3 months were significantly associated with stronger clinical improvements at 3-months for both AS and PsA patients (AS: $\beta_{\Delta gSUVmax}$ = 8.5, p<0.001; PsA: $\beta_{\Delta gSUVmax}$ = 20.0, p<0.001), and these improvements were sustained at 6 months follow-up (Figure 2D-E).

Prediction of clinical progression

Finally, we explored whether baseline $gSUV_{max}$ was associated with subsequent changes in disease activity at 3- and 6-months follow-up after the initiation of biologics. Among AS participants, lower baseline $gSUV_{max}$ were nominally associated with stronger reductions in disease activity during follow-up, although the associations were not statistically significant (Figure 3A). No statistically significant associations between baseline $gSUV_{max}$ and changes in disease activity was found for PsA participants (Figure 3B).

Discussion

The present study investigated the ability of ^{18}F-FDG PET to track disease activity, both cross-sectionally and longitudinally, in AS and PsA patients who were candidates for initiation of biologic therapy. We found that ^{18}F-FDG uptake in clinically involved joints/entheses was strongly correlated with pre-treatment disease activity in patients with AS. This result was supported by our longitudinal analysis, in which we confirmed that more pronounced decreases in ^{18}F-FDG uptake were significantly associated with better responses to biologic treatment, both in AS and PsA participants. Together, our findings

indicate that ^{18}F-FDG PET may be a useful tool for objective monitorisation of disease activity and assessment of treatment response in AS and PsA patients undergoing therapy with biologics.

A number of prior cross-sectional studies investigated the ability of ^{18}F-FDG PET for the detection of lesions in patients with AS (16–18, 25). However, the potential of ^{18}F-FDG PET as an objective marker of disease activity in AS remains largely unexplored, with only two case reports ($n \leq 3$ participants, (30, 31)) suggesting potential of ^{18}F-FDG PET to monitor treatment effects in patients with AS. Here, we provide the largest analysis to date supporting this notion. By performing quantification of ^{18}F-FDG uptake, we first demonstrated that clinically involved joints/entheses showed a statistically significant increase of 30% in ^{18}F-FDG uptake compared to uninvolved regions. Although this result aligns well with findings from previous reports (16–18), a previous study showed no elevations in ^{18}F-FDG uptake in 10 out of 12 AS patients (25). These conflicting results are, however, likely explained by differences in the characteristics of the AS population studied in (25), which includes patients with low disease activity (n = 5) and an overall milder inflammatory state (only 3 of these patients showed bone edema on MRI). Despite this controversy, our study provides novel evidence supporting the ability of ^{18}F-FDG PET to capture disease-related inflammatory processes. We found that pre-treatment ^{18}F-FDG uptake in the clinically involved joints/entheses, as measured with the composite measure $gSUV_{max}$, was strongly correlated with pre-treatment disease activity, as reflected by the ASDAS score. Furthermore, we confirmed this cross-sectional result in the longitudinal analysis, which showed that larger clinical benefits were accompanied by larger decreases in ^{18}F-FDG uptake of the clinically involved joints/entheses. Our results suggest that ^{18}F-FDG PET may be a useful marker of disease activity in AS patients with clinically active disease. ^{18}F-FDG PET may also have a relevant application for tracking treatment effects in therapeutic trials or clinical settings.

The pattern of findings in our PsA cohort is less clear, though still consistent with our findings in AS patients. We found that clinically involved joints/entheses displayed ~ 25% higher ^{18}F-FDG uptake compared to unaffected regions; however, we did not find a statistically significant association between pre-treatment ^{18}F-FDG uptake and disease activity. This result may be explained by the lower sample size of the PsA group (n = 8) together with the relatively homogeneous distribution of DAPSA scores (range: [18–34]), which may result in a limitation of the power to detect a statistical association. Yet, in line with our findings in AS patients, we did find a statistically significant association between stronger clinical improvements and longitudinal decreases in ^{18}F-FDG uptake in the affected regions. Together, these findings extend previous results indicating that ^{18}F-FDG PET can capture inflammatory processes in PsA (22), and support the notion that this imaging modality may also represent a useful marker of disease activity and treatment effectiveness. However, additional studies with larger sample sizes and wider range of baseline disease activity are needed to confirm these results.

Interestingly, we did not find a statistically significant association between pre-treatment ^{18}F-FDG uptake and clinical response to biological treatment at follow-up. This result resonates with findings from

previous studies using ^{18}F-NaF PET, in which pre-treatment uptake was not predictive of clinical response to TNFα antagonist therapy (26). These results suggest that the factors that influence the likelihood of clinical response are not fully captured by PET imaging with ^{18}F-FDG or ^{18}F-NaF. Nevertheless, it is still possible that pre-treatment ^{18}F-FDG uptake could be predictive of clinical response in different patient populations, in particular in those at a more severe disease stage. Given that ^{18}F-FDG uptake correlates well with disease activity, it is likely that higher pre-treatment ^{18}F-FDG uptake may be associated with better clinical response, as patients with high baseline disease activity tend to respond better to biological treatment (32). Further studies are warranted to clarify the power of ^{18}F-FDG PET to predict clinical response in AS and PsA patients undergoing therapy with biologics.

The present study had a number of limitations. First, although relatively large for a PET imaging study on AS and PsA patients, the sample size of our study was modest, particularly for the longitudinal analysis. Second, our inclusion criteria led to relatively homogenous clinical characteristics for our study participants. This may have limited our statistical power to detect associations between ^{18}F-FDG PET and disease severity scores. The performance of ^{18}F-FDG PET may also vary for more diverse patient populations. Third, study participants underwent different treatment regimes, which might have influenced our longitudinal findings. Fourth, due to low the sample size in, we were underpowered to analyse how ^{18}F-FDG uptake in specific joints/entheses influenced clinical outcomes.

In summary, we provided first-time evidence suggesting that ^{18}F-FDG PET is an accurate marker of disease activity in patients with AS and PsA. Our findings suggest that ^{18}F-FDG PET may be a useful surrogate marker of treatment effectiveness in therapeutic trials for AS or PsA, and may provide valuable information to clinicians evaluating clinical response to biologic treatments.

Abbreviations

AS: Ankylosing spondylitis.

BASDAI: Bath Ankylosing Spondylitis Disease Activity Index.

DAPSA: Disease Activity Index for Psoriatic Arthritis.

DMARDs: Disease-modifying antirheumatic drugs.

$gSUV_{max}$: global SUV_{max}.

LME: Linear mixed-effects.

MRI: Magnetic resonance imaging.

NaF: ^{18}F-sodium fluoride.

NSAIDs: Non-steroidal anti-inflammatory drugs.

PET: Positron emission tomography.

PsA: Psoriatic arthritis.

r: Correlation coefficient.

ROI: Region of interest.

SpA: Seronegative spondyloarthropathies.

SUV_{max}: Maximum standardized uptake value.

Declarations

DISCLOSURES

Nothing to disclose.

DATA AVAILABILITY

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

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Figures

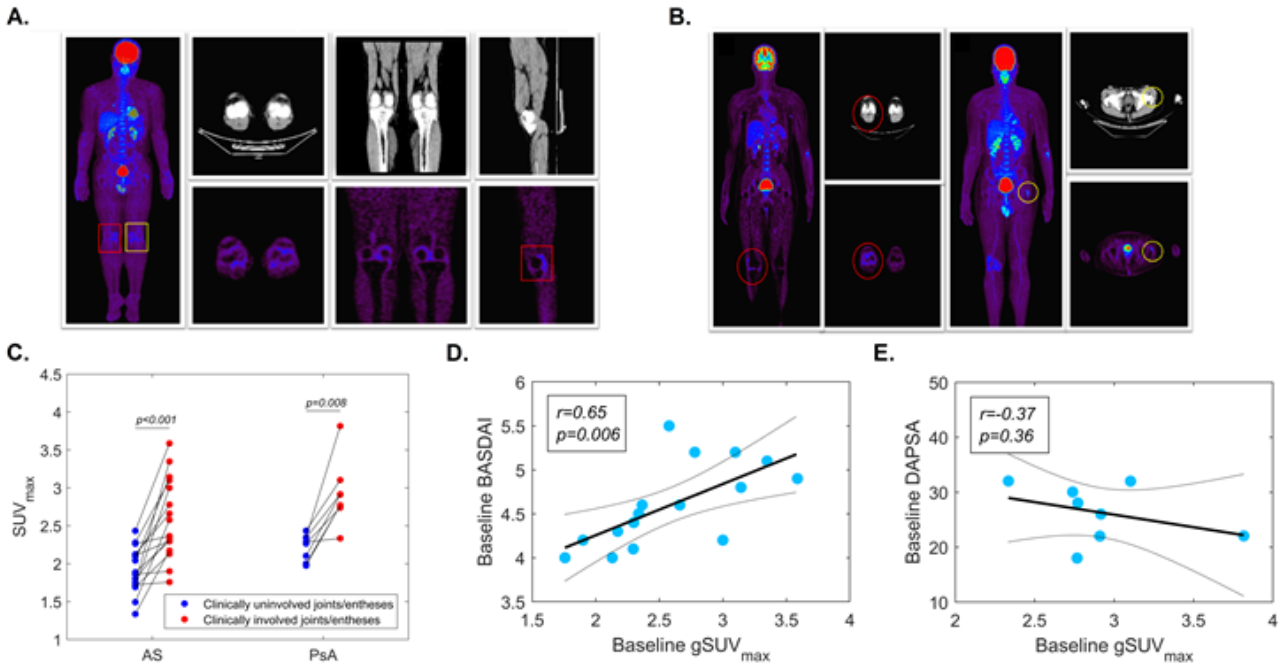

Figure 1

Pre-treatment relationships between ^{18}F-FDG uptake in clinically affected joints/entheses and disease activity. A) Example of an AS patient displaying elevated ^{18}F-FDG uptake at the knees. B) Example of a PsA patient displaying ^{18}F-FDG uptake at the right knee and left trochanter areas. C) Comparison of ^{18}F-FDG uptake in clinically involved vs clinically uninvolved joints/entheses. Reported p-values are from sign tests comparing the median ^{18}F-FDG uptake between the involved/uninvolved regions. D) and E) represent the associations between ^{18}F-FDG uptake, as measured using the composite score $gSUV_{max}$, and disease activity in AS (D) and PsA (E). Correlation coefficients (r), together with respective p-values, are reported in the boxes.

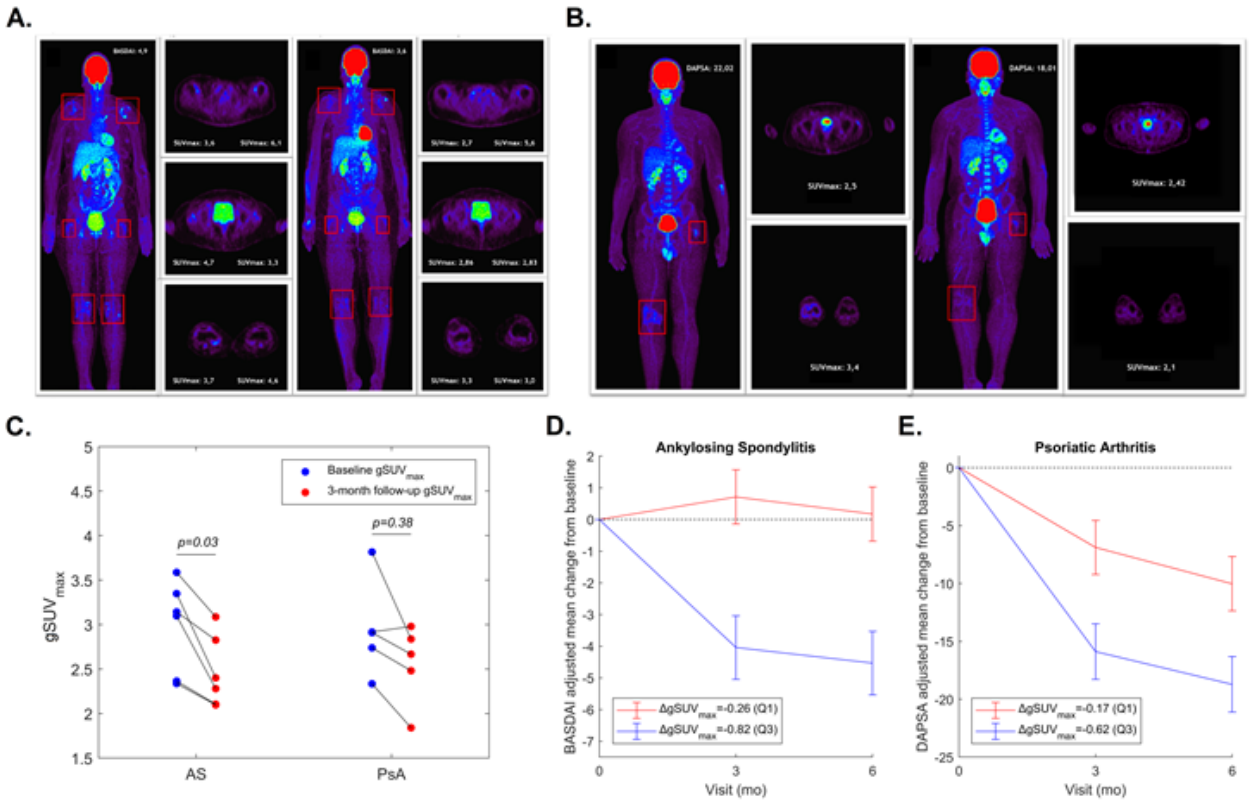

Figure 2

Longitudinal relationships between ^{18}F-FDG uptake in clinically affected joints/entheses and disease activity. A) and B) Example of pre-treatment vs 3-month post-treatment ^{18}F-FDG PET scans of an AS (A) and PsA (B) patient. For the AS patient (A), the pre-treatment scan shows elevated ^{18}F-FDG uptake at the clinically involved areas (shoulders, knees, and hips). After 3 months of biologic treatment, the follow-up ^{18}F-FDG PET scan shows clear reductions in ^{18}F-FDG uptake in the aforementioned regions. For the PsA patient (B), the pre-treatment scan showed elevated ^{18}F-FDG uptake at the right knee and left trochanter areas. After 3 months of treatment with biologics, the follow-up scan revealed significantly lower ^{18}F-FDG uptake in the knee and slightly lower uptake in the trochanter area. C) Comparison of ^{18}F-FDG uptake, as measured using gSUV$_{max}$, before and 3 months after treatment. Reported p-values are from sign tests comparing the median gSUV$_{max}$ between the pre- and post-treatment scans. D) and E) Results from linear mixed effects models showing the adjusted mean change from baseline in ASDAS for AS (D) and in DAPSA for PsA (E) at 3 and 6 months after biological treatment initiation. Results are shown for the first (Q1) and third quartile (Q3) of the 3-month change in gSUV$_{max}$. Stronger reductions in gSUV$_{max}$ (Q3) were associated with greater clinical improvements at follow-up (blue lines).

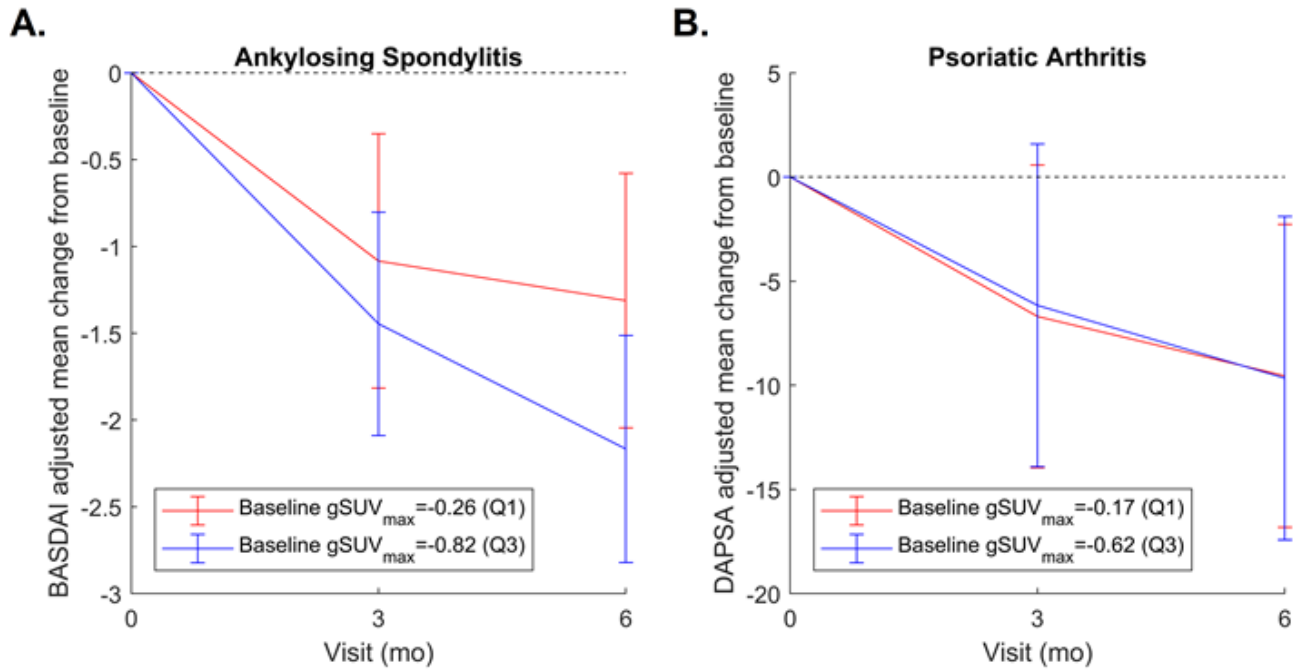

Figure 3

Results from linear mixed effects models showing the adjusted mean change from baseline in ASDAS for AS (A) and in DAPSA for PsA (B) at 3 and 6 months after biological treatment initiation. Results are shown for the first (Q1) and third quartile (Q3) of the pre-treatment $gSUV_{max}$. No statistically significant associations between pre-treatment $gSUV_{max}$ and clinical improvements at follow-up were found.