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Original article

# Quantitative Metabolic Volumetric Product on $^{18}$Fluorine-2fluoro-2-deoxy-D-glucose-positron Emission Tomography/Computed Tomography in Assessing Treatment Response to Disease-modifying Antirheumatic Drugs in Rheumatoid Arthritis: Multiparametric Analysis Integrating American College of Rheumatology/European League Against Rheumatism Criteria

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## Abstract

The purpose of this study was to assess the role of fluoro-2-deoxy-D-glucose-positron emission tomography/computed tomography (FDG-PET/CT) in the evaluation of treatment response evaluation to disease-modifying antirheumatic drug (DMARD) therapy in patients of rheumatoid arthritis (RA). A total of ten patients with proven diagnosis of RA as per the 2010 American College of Rheumatology/European League against Rheumatism (EULAR) criteria were prospectively evaluated. All patients underwent clinical and biochemical evaluation and a baseline FDG-PET/CT with assessment of maximum standardized uptake value and metabolic volumetric product (MVP) values. DMARD therapy was started with a combination of hydroxychloroquine and sulfasalazine. On follow-up at 3 and 6 months, the response to treatment was assessed by clinical, biochemical, and FDG-PET/CT parameters. These parameters were analyzed in a combined manner, and the patients were grouped into 4 categories as per response to DMARD therapy - complete response, good response, mixed response, and no response. Evaluation of treatment response in ten patients at 3$^{rd}$ month and in nine patients at 6 months showed (a) agreement for MVP, biochemical parameters with clinical symptomatic assessment in all patients, (b) while agreement for EULAR score was noted in only three patients and disagreement in seven patients with clinical symptoms Response EULAR (rEULAR) (0.37) and at 6 months in only three patients and disagreement in six patients, rEULAR (0.52). The correlation factors at 3$^{rd}$ month and 6$^{th}$ months were, respectively, as follows: rMVP (0.67 and 0.75), response RA factor (0.54 and 0.74), response erythrocyte sedimentation rate (0.81 and 0.73), response C-reactive protein (0.78 and 0.51), and response anti-cyclic citrullinated peptide antibodies (0.33 and 0.54). The overall response to DMARD therapy at 3 months was assessed with results showing good response by four cases (40%), mixed response by 1 (10%), no response by 5 (50%), and complete response by none (0%). Step-up therapy at 3 months was initiated in four

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patients showing nonresponse/progression on clinical symptomatic assessment; of these, two patients showed a good response, one mixed response, and the remaining one continued to show nonresponse at 6 months follow-up. One patient who had a minimal response at 3 months on PET-CT (only 5.96% reduction of MVP) was continued on the same DMARD in view of clinical symptomatic good response (at 3 months) but ultimately had disease progression in all scales and worsening of symptom (at 6 months). FDG-PET/CT-based assessment of inflammatory activity noted in the joints of RA with quantitative parameters can be a promising approach for the whole body assessment of RA disease activity and treatment response assessment, especially in inconclusive cases and correlates well with other parameters. MVP can be used as a useful objective and adjunct parameter for assessing response to treatment.

**Keywords:** $^{18}$Fluorine-2fluoro-2-deoxy-D-glucose-positron emission tomography/computed tomography, 2010 American College of Rheumatology/European League Against Rheumatism rheumatoid classification criteria, disease-modifying antirheumatic drugs, metabolic volumetric product, rheumatoid arthritis

## Introduction

In the present era of a number of new diagnostic modalities for disease detection and underlying pathological evaluation, positron emission tomography-computed tomography (PET-CT) has evolved as one of the new promising radiological and molecular imaging diagnostic technologies to detect molecular pathology of many underlying conditions including infection and inflammation of joints and ligaments as well. One of the merits of PET-CT is that it enables quantitative measurement of metabolic activity. $^{18}$Fluorine-2fluoro-2-deoxy-glucose-PET-CT ($^{18}$F-FDG PET-CT) studies have been proposed to assess the metabolic activity measured quantitatively by the standardized uptake value (SUV) of articular lesions in patients with rheumatoid arthritis (RA).[1-8]

RA is an autoimmune disorder that results in chronic, systemic inflammatory affection of many tissues and organs, but principally involves flexible (synovial) joints. It can be a disabling and painful condition with substantial loss of functioning and can limit daily activities in these patients, with a significant burden in terms of health-care management and costs. The main pathological manifestations of RA include synovitis, pannus formation, and bone erosion. These pathological changes are usually assessed by plain X-ray, ultrasonography, CT, and contrast-enhanced, fat-suppressed magnetic resonance imaging. PET/CT with $^{18}$F-FDG can be used to evaluate the metabolic activity of synovitis and measure the disease activity in RA patients with added advantage of whole-body imaging.[9-11] Imaging studies using $^{18}$F-FDG-PET/CT have been performed to assess the metabolic activity of synovitis in patients of RA and thereby evaluate the disease activity of RA. Various study 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.[1-8]

One of the merits of PET/CT is that it enables quantitative measurement of metabolic activity and provides whole body objective assessment in a single examination. $^{18}$F-FDG-PET/CT studies have been proposed to assess the metabolic activity measured quantitatively by the SUV routinely. Metabolic volumetric product (MVP) is a new quantitative estimate used to calculate the amount of global metabolic activity in the lesion.[12-15] This quantitative parameter can be potentially used to evaluate response following administered therapy and can serve as an objective imaging adjunct along with clinical assessment and biochemical markers in RA patients receiving disease modifying antirheumatic drugs (DMARDs) therapy.

## Materials and Methods

This prospective pilot study protocol was approved by the Institutional Medical Ethics Committee and was undertaken over a period of 18 months.

### Patient inclusion criteria

Newly diagnosed patients of RA as per the 2010 American College of Rheumatology/European League against Rheumatism (ACR/EULAR) rheumatoid classification criteria, who were being considered for being put on DMARDs by the clinician were included in this prospective research study.

### Patient exclusion criteria

Previously treated cases and pregnancy were excluded from the study. Patient's inability to lie still for the duration of the PET-CT acquisition (around 30 min) and history of claustrophobia were considered as relative exclusion criteria.

All eligible patients were explained about the procedure in detail regarding both benefits of the test and possible adverse effects of radiation. Written informed consent was taken before the administration of radionuclide. The patients underwent routine workup including clinical examination and biochemical tests at the rheumatology clinic. All relevant study data from the detailed study pro forma were entered into an excel sheet for subsequent

analysis. The patients were inquired about their symptoms (swollen joints, deformities, rise of temperature, and pain on movement) and its duration. They underwent routine biochemical investigations including C-reactive protein (CRP), rheumatoid factor (RF), anti-cyclic citrullinated peptide (CCP) antibodies, and erythrocyte sedimentation rate (ESR) to assess the inflammatory status. EULAR score for each individual was then calculated and noted. Patients subsequently underwent $^{18}$F-FDG whole body PET-CT before starting treatment with DMARDs. Joints involved on FDG-PET/CT were noted, and correlation with the symptoms and clinical assessment was undertaken. SUVmax and MVP of the involved joints were calculated and noted.

## Fluoro-2-deoxy-D-glucose-positron emission tomography/computed tomography imaging acquisition and analysis

The patients fasted for at least 6 h before injection and were at rest for 15 min to reduce muscular uptake. Before injecting the tracer, the blood glucose level was measured in all patients and did not exceed 140 mg/dL. $^{18}$F-FDG (5 MBq/kg) was injected in a peripheral vein through an indwelling catheter. On the basis of previous time course studies, whole-body imaging including fingers and toes was initiated at least 45 min after injection of the radiotracer, with a mean time of 73 min (range, 51–100 min) using PET-CT scanner Gemini TF PET/CT (Philips Medical Systems, USA). Patients were positioned in a supine position and knees were positioned in the axial plane of the tomographic gantry, centered in the field of view. Separate view is taken for the upper limbs of obese patients whose upper limbs could not be imaged properly in the whole body scan. Reconstruction of images was done using RAMLA algorithm. FDG uptake was evaluated by the SUVmax in the corresponding symptomatic joints. MVP and metabolic tumor volume (MTV) were measured using a volume viewer software (popularly known as tumor-tracking software, an integrated automated software in the Philips Gemini TF PET/CT (Philips Medical Systems, USA), which provides an automatically delineated volume of interest (VOI) using an isocontour threshold method based on SUV. Using a predefined threshold SUV of 1.5, VOIs of the lesions were automatically generated, referred to as the metabolic volume. Any extra-articular lesions detected such as lymph nodal involvement or lung involvement were noted in every patient. MVP (in the form of metabolic index [max]) was calculated by the automated tumor tracking software (which is theoretically the sum total

**Table 1: Response categorization based on 2 fluoro-2-deoxy-glucose-positron emission tomography-computed tomography, biochemical parameters, and clinical assessment**

| Response evaluation | At 3 months | At 6 months |
|---|---|---|
| Clinical evaluation | Assessing pain relief as percentage compared to initial pretreatment symptoms. New joint involvement was inquired and noted | Assessing pain relief as percentage compared to initial pretreatment. New joint involvement was inquired and noted |
| Biochemical evaluation | Percentage reduction of anti-CCP, CRP, ESR, and RF titers as compared to baseline | Percentage reduction of anti-CCP, CRP, ESR, and RF titers as compared to baseline |
| PET-CT evaluation | Percentage reduction in $SUV_{max}$, MVP as compared to baseline scans | Percentage reduction in $SUV_{max}$, MVP as compared to baseline scans |
| EULAR score evaluation | Percentage change in EULAR score as compared to baseline score | Percentage change in EULAR score as compared to baseline score |

| Response | PET-CT scan | Biochemical findings | Clinical findings | Change of DMARDs at the clinic |
|---|---|---|---|---|
| Complete response | Visually scan shows no enhanced uptake with $SUV_{max}$ and MVP significantly reduced no new joints seen visually | All the biochemical findings are under normal values | Patients are asymptomatic in the joints they complained previously | No |
| Good response | Visually still enhanced uptake observed in known involved joints, but there is >50% reduction in the MVP; no new joints visually | Biochemical values are reduced but still above normal | Patients have their symptoms reduced, but still persisting in some joints. No new joints seen | No |
| Mixed response | PET-CT scan showed moderate to minimal (25%-50%) reduction in $SUV_{max}$, MVP in previous joints without any involvement of new joints compared to baseline; or reduction in $SUV_{max}$ and MVP with appearance of new joints which were not seen in baseline scan | Minimal to moderate reduction or almost the same values of biochemical investigations, and above normal range | Some joints show response/ asymptomatic while others show persistent pain +/− new joints appearing | Step up therapy: DMARDs can be continued with increase in dosage/ change of DMARD drugs or addition of new drugs |
| No response | PET-CT findings show almost similar or increase in the value of $SUV_{max}$ in the old joints seen in baseline scan; new joints appearing | Increase in the value of biochemical parameters | Symptoms not relieved and new joints appearing | Change of DMARDs/ addition of other DMARDs-step-up therapy |

EULAR: European League Against Rheumatism; RF: Rheumatoid factor; CRP: C-reactive protein; Anti-CCP: Anti-cyclic citrullinated peptide; ESR: Erythrocyte sedimentation rate; DMARDs: Disease-modifying anti-rheumatic drugs; PET-CT: Positron emission tomography-computed tomography; MVP: Metabolic volumetric product; $SUV_{max}$: Maximum standardized uptake value

**Table 2: Comparison of response based on clinical variables, quantitative positron emission tomography, biochemical parameters, and European League Against Rheumatism score at 3-month follow-up**

| Cases | Clinical response (%) | MVP response (%) | EULAR score response (%) | Biochemical response (%) |
|---|---|---|---|---|
| 1 | 50 | 66.05 | 0 | RA: 98.5<br>ESR: 66<br>CRP: 36.11<br>Anti-CCP abs: 7.5 |
| 2 | 57 | 5.96 | 28.5 | RA: 29.13<br>ESRL: 81.9<br>CRP: 12.5<br>Anti-CCP abs: 70.4 |
| 3 | −18 | −127 | 0 | RA: 45.8<br>ESR: 43.1<br>CRP: 25.60<br>Anti-CCP abs: 2.04 |
| 4 | 60 | 53.2 | 0 | RA: 44.2<br>ESR: 37.5<br>CRP: 33.3<br>Anti-CCP abs: 22.68 |
| 5 | 75 | 87 | 0 | RA: 62.1<br>ESR: 55.35<br>CRP: 52.64<br>Anti-CCP abs: 30.2 |
| 6 | −30 | −163.5 | 0 | RA: 49.1<br>ESR: 22<br>CRP: 54.9<br>Anti-CCP abs: 0 |
| 7 | −84 | −37 | 0 | RA: 9.4<br>ESR: 29<br>CRP: 38<br>Anti-CCP abs: 15.5 |
| 8 | −10 | −243.6 | 0 | RA: 2.8<br>ESR; 20<br>CRP: 29.2<br>Anti-CCP abs: 218.7 |
| 9 | 20 | 33.5 | 20 | RA: 25.8<br>ESR: 48<br>CRP: 49.6<br>Anti-CCP abs: 49.1 |
| 10 | 60 | 84.6 | 20 | RA: 58.6<br>ESR: 67.8<br>CRP: 49.1<br>Anti-CCP abs: 53 |

EULAR: European League Against Rheumatism; MVP: Metabolic volumetric product; RA: Rheumatoid arthritis; CRP: C-reactive protein; Anti-CCP: Anti-cyclic citrullinated peptide; ESR: Erythrocyte sedimentation rate

**Table 3: Comparison of response based on clinical variables, quantitative positron emission tomography, biochemical parameters, and European League Against Rheumatism score at 6-month follow-up**

| Cases | Clinical response (%) | MVP response (%) | EULAR score response (%) | Biochemical response (%) |
|---|---|---|---|---|
| 1 | 66.6 | 75.2 | 0 | RA: 93.1<br>ESR: 51.3<br>CRP: 41.6<br>Anti-CCP abs: 37 |
| 2 | −18 | −16.83 | 0 | RA: 10<br>ESR: 52.7<br>CRP: 97<br>Anti-CCP abs: 62 |
| 3 | 76 | 94.6 | 11.0 | RA: 70.7<br>ESR: 81.4<br>CRP: 70.83<br>Anti-CCP abs: 61.2 |
| 4 | 40 | 45.7 | 0 | RA: 8.83<br>ESR: 25.2<br>CRP: 65.47<br>Anti-CCP abs: 21.64 |
| 5 | 57 | 30.2 | 0 | RA: 49.42<br>ESR: 71.42<br>CRP: 81.64<br>Anti-CCP abs: 37.2 |
| 6 | −30 | −266.9 | 0 | RA: 35.6<br>ESR: -25.8<br>CRP: -39.6<br>Anti-CCP abs: 30 |
| 7 | −8.9 | −24 | 0 | RA: 9.4<br>ESR: 29<br>CRP: 38<br>Anti-CCPs: 15.5 |
| 8 | −50 | −872 | −20 | RA: 2.8<br>ESR: 20<br>CRP: 29.2<br>Anti-CCPs: 147 |
| 9 | 70 | 52.7 | 20 | RA: 61.3<br>ESR: 83.3<br>CRP: 63.8<br>Anti-CCPs: 92.1 |

EULAR: European League Against Rheumatism; MVP: Metabolic volumetric product; RA: Rheumatoid arthritis; CRP: C-reactive protein; Anti-CCP: Anti-cyclic citrullinated peptide; ESR: Erythrocyte sedimentation rate

of individual products of SUVmax obtained per slice of ROI and that ROI volume calculated by multiplying the area of ROI by the slice thickness).

Patients were then started on DMARD therapy (with a combination of hydroxychloroquine and sulfasalazine) based on the clinical assessment, biochemical evaluation symptoms, and scan findings. They were advised to note about the response of the treatment given and the extent of pain relief. All patients were inquired about the treatment dosage, regularity, and side effects occurred during the period, and these observations were noted. Treatment regimens with new drugs were added to those patients who were not responding to the previous drugs and to the patients who showed new joint involvement. A follow-up clinical evaluation, FDG PET-CT study, and

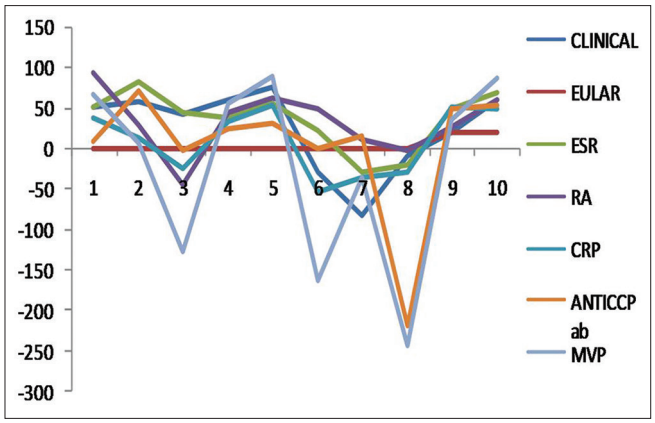


**Figure 1:** Response evaluation at 3 months-line diagram, x-axis showing patients and y-axis showing % response

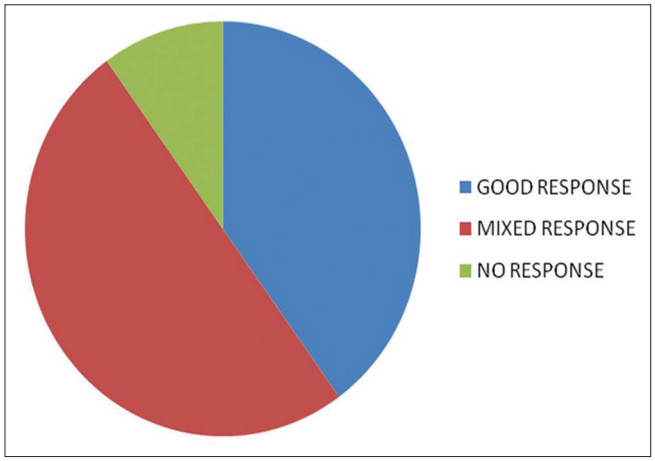


**Figure 3:** Overall response

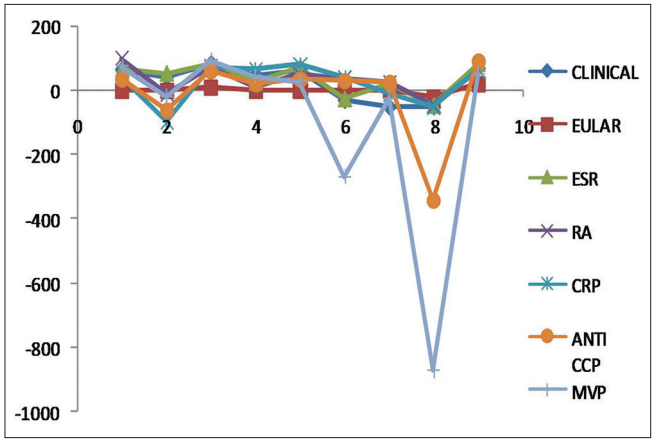


**Figure 5:** Scatter plot diagram of response variables at second follow-up (6 months)

biochemical tests were done at 3 and 6 months to assess the treatment response.

The results were analyzed and compared multiparametrically at 3 months and 6 months as follows in below-mentioned Table 1.

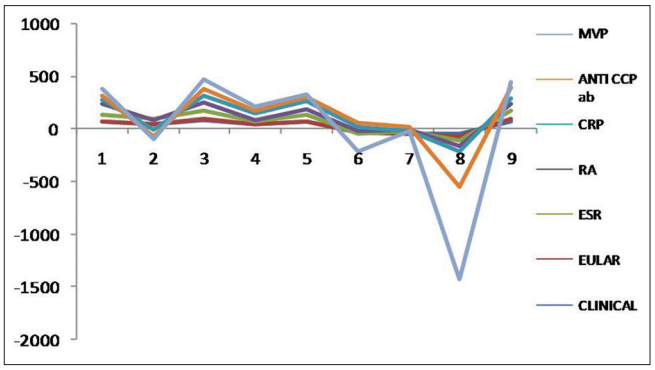


**Figure 2:** Response evaluation at 6 months-line diagram, x-axis showing patients and y-axis showing % response

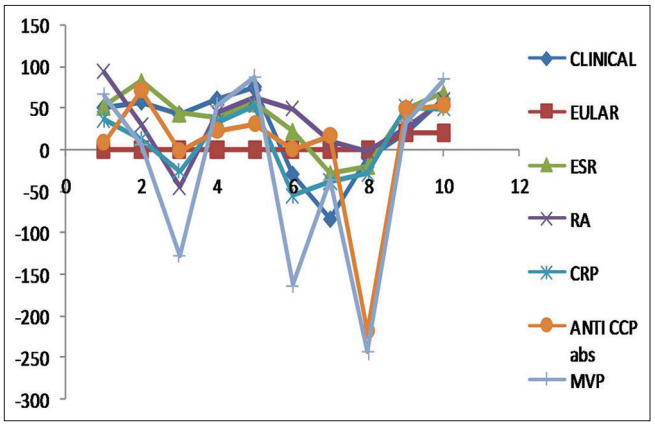


**Figure 4:** Scatter plot diagram of response variables at first follow-up (3 months)

**Table 4a: Overall response evaluation at 3 months to first line disease-modifying antirheumatic drugs therapy**

| Overall response | Number of patients |
|---|---|
| Good response | 4 |
| Mixed response | 1 |
| Complete response | 0 |
| No response | 5 |

**Table 4b: Overall response evaluation at 6 months to step-up therapy in four patients with no response at 3 months**

| Patient ID | Response to step-up therapy |
|---|---|
| 3 | Good (−127% to+94.6%=>50%) |
| 6 | No (−163.5% to−266.9%) |
| 7 | Mixed (−37% to−24%=13%) |
| 8 | No (−243.6% to−872%) |

A correlation analysis of the following calculated parameters was undertaken at the first and second follow-up:

1. Clinical symptomatic response and PET-CT scan response with MVP
2. Clinical symptomatic response with biochemical response

3. Clinical symptomatic responses with EULAR score response
4. Calculating the Pearson's correlation coefficient and sensitivity of MVP over biochemical and EULAR score.

All the parameters which showed positive correlation are plotted on + X, +Y regions of the graph. The parameters which showed negative correlation are plotted on + X, −Y regions of the graph. An estimation of Pearson's correlation coefficient of each parameter calculated against clinical symptomatic response was undertaken. In addition, identification of extra-articular lesions other than the articular lesions involved was also observed and assessed.

## Results

A total of 12 patients with RA were prospectively enrolled over the study period. Of the 12, ten patients (10 females, aged 33–75 years; mean 49 years, standard deviation - 7.6) had undergone all three scans with the other set of parameters and two patients were lost to follow-up. The baseline RF factor was positive for all patients and other biochemical parameters raised as per ACR/EULAR criteria. All patients had more than five joints involvement at the baseline and diagnosed as RA. The percentage change (from the baseline) in clinical assessment, biochemical parameters, scan response MVP (rMVP), and EULAR score in each individual has been detailed in comparative columns in Table 2 (at 3 months) and Table 3 (at 6 months).

**Table 5: Correlation coefficients of response variables at follow-ups**

| Follow-up | MVP response versus clinical response (rMVP) | EULAR response versus clinical response (rEULAR) | Biochemical response versus clinical response |
|---|---|---|---|
| First follow-up | 0.67 | 0.37 | rRA factor: 0.54<br>rCRP: 0.78<br>rESR: 0.81<br>rAnti-CCP abs: 0.33 |
| Second follow-up | 0.75 | 0.52 | rRA factor: 0.74<br>rCRP: 0.51<br>rESR: 0.73<br>rAnti-CCP abs: 0.54 |

EULAR: European League Against Rheumatism; MVP: Metabolic volumetric product; rEULAR: Response EULAR; rMVP: Response MVP; rRA: Response rheumatoid arthritis; rCRP: Response C-reactive protein; rAnti-CCP: Response anti-cyclic citrullinated peptide; rESR: Response erythrocyte sedimentation rate

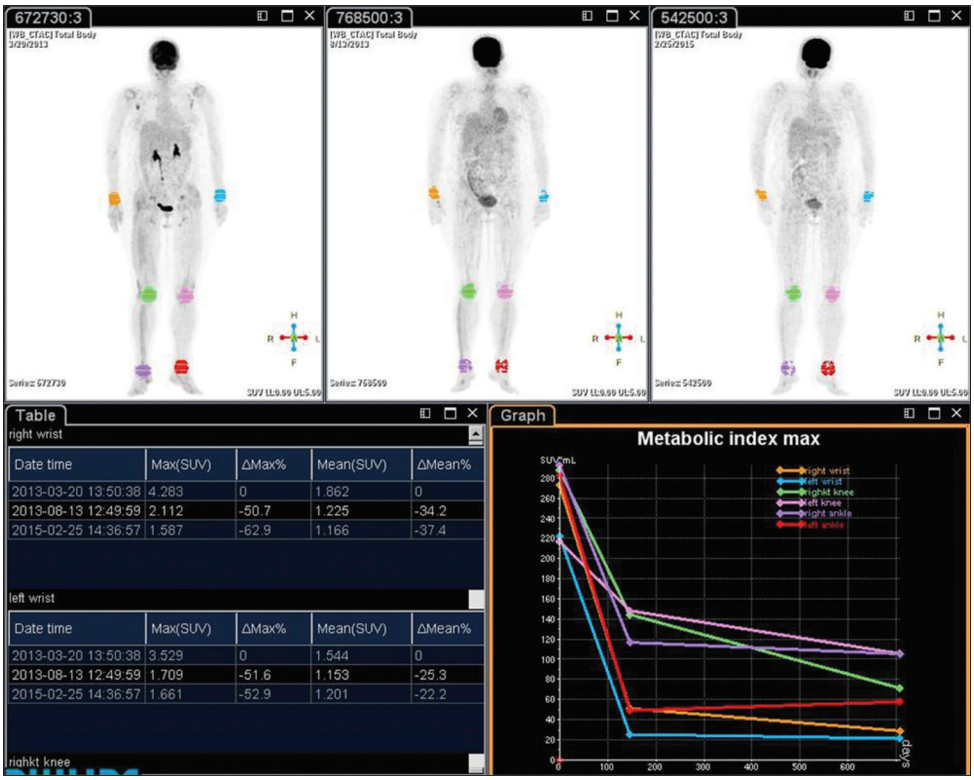


**Figure 6:** The fluoro-2-deoxy-D-glucose-positron emission tomography/computed tomography scan showing overall good response. The upper three images are the maximum intensity projection images (at baseline, 3, and 6 months from left to right) showing the joint involvement and extra-articular lesions including bilateral axillary nodes and inguinal nodes at baseline study. There is a good response noted in the joints in the subsequent follow-ups. The lymph nodes also showed a significant response with no uptake in the follow-up scans. The metabolic volumetric product response (in the form of metabolic index max) response is depicted graphically as shown by the curves

All the parameters were depicted graphically (plot of response variables) at first and second follow–up, respectively [Figures 1 and 2]. The clinical response and rMVP were in concordance in all the patients, whereas the individual biochemical parameters response and combined EULAR response were in discordance in few patients [Tables 2 and 3], likely related to the fact that biochemical parameters are not specific to RA only and could vary in many other pathological conditions.

The overall response to DMARD therapy at 3 months [Table 4a and Figure 3] was assessed with results showing good response by four cases (40%), mixed response by 1 (10%), no response by 5 (50%), and complete response by none (0%).

**Table 6: Additional features**

| Additional features | | | Number of patients |
|---|---|---|---|
| Number of patients showed new joint involvement throughout the study | | | 1 |
| Step-up therapy used for | | | 2 |
| Number of patients showed extra-articular pathology | | | 1 |
| **Lymph nodes involved** | **Baseline $SUV_{max}$** | **First follow-up** | **Response (%)** |
| Right axillary node | 4.12 | - | 100 |
| Left axillary node | 3.86 | - | 100 |
| Right inguinal node | 3.2 | - | 100 |

$SUV_{max}$: Maximum standardized uptake values

Step-up therapy at 3 months was initiated in four patients showing nonresponse/progression on clinical symptomatic assessment in the form of addition of methotrexate: of these, two patients showed a good response, one mixed response, and the remaining one continued to show nonresponse at 6 months follow-up clinical, PET-CT, and biochemical evaluation [Table 4b]. Interestingly, one patient (patient 2) who had minimal response at 3 months on PET-CT (only 5.96% reduction of MVP) was continued on the same DMARD in view of clinical symptomatic good response (at 3 months) but ultimately had disease progression and worsening of symptom in all scales (at 6 months).

One of the ten patients whose baseline FDG-PET/CT showed axillary lymph nodal inflammation showed marked reduction in the inflammation and good response to the DMARDS given when compared to the baseline study.

In the first follow-up evaluation, in all ten patients, the results of therapeutic response evaluation showed

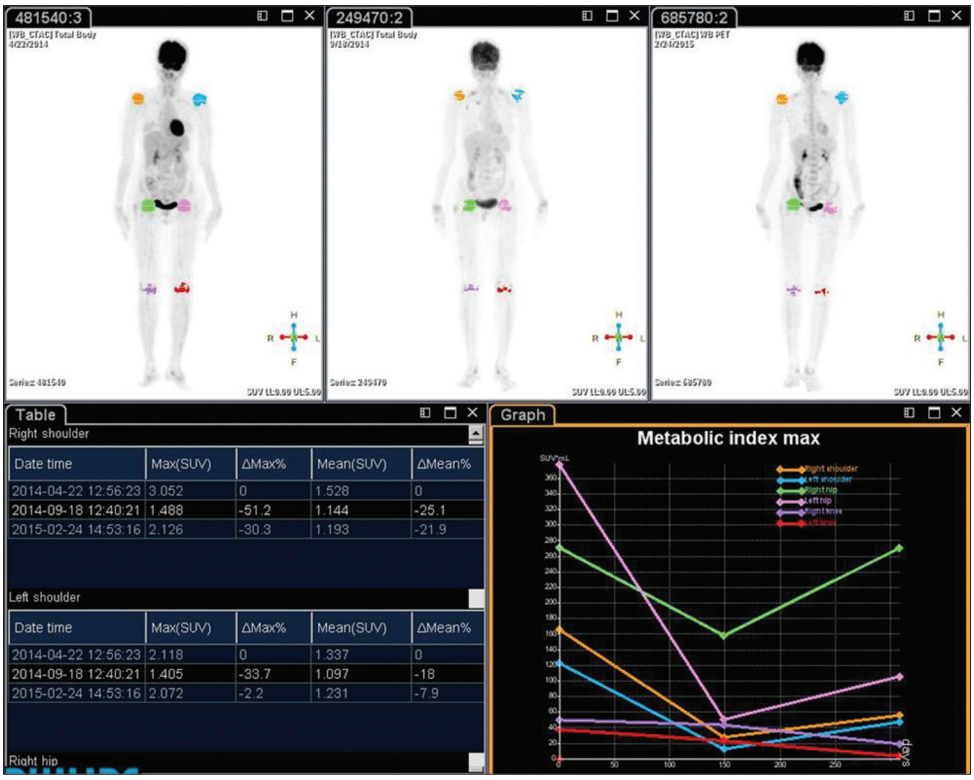


**Figure 7:** Fluoro-2-deoxy-D-glucose-positron emission tomography/computed tomography scan showing response followed by recurrence. The upper three images are maximum intensity projection images showing the joint involvement at baseline, 3, and 6 months. There was initially good response noted in the first follow-up (middle image). After getting relief, the patient was irregular in taking disease-modifying antirheumatic drugs; subsequently, the joints showed increase in the inflammation and clinical symptoms. This was clearly assessed by the maximum standardized uptake value and metabolic volumetric product on the positron emission tomography-computed tomography scan. The response is depicted graphically as shown by the curves


**Figure 8:** The fluoro-2-deoxy-D-glucose-positron emission tomography/computed tomography showing initial nonresponse followed by response to step-up therapy. The upper three images are maximum intensity projection images showing the joint involvement at baseline, 3, and 6 months. There is increase in the active inflammation noted in the joints in the first follow-up which showed rise in the curve to a different extent in different joints. This patient was advised etoricoxib, hydroxychloroquine after the baseline scan. After first follow-up, in this patient, step-up therapy was used with methotrexate. The subsequent scan showed a good response. The response is depicted graphically as shown by the curves

agreement for (1) MVP on PET-CT scan and clinical symptomatic assessment, (2) biochemical parameters and clinical response assessment, (3) while agreement for EULAR score was noted only in three patients and disagreement in seven patients. Significant correlation was noted with MVP (rMVP-0.67) while other parameters correlation factors were as follows: response EULAR (rEULAR) (0.37), rRA factor (0.54), rESR (0.81), rCRP (0.78), and rAnti-CCP antibodies (0.33) [Figure 4 and Table 5]. In the second follow-up evaluation, undertaken in nine patients, the results of therapeutic response evaluation showed agreement for (1) MVP on PET-CT scan and clinical symptomatic assessment, (2) biochemical parameters and clinical response assessment, (3) while agreement for EULAR score was noted in three patients and disagreement in six patients. Significant correlation is noted with MVP (rMVP-0.75), while for the other parameters, the correlation factors were rEULAR (0.52), rRAfactor (0.74), rESR (0.73), rCRP (0.51), and rAnti-CCP antibodies (0.54) [Figure 5 and Table 5].

We noted bilateral axillary and right inguinal lymph nodal FDG uptake in one patient in addition to the articular lesions at baseline, probably depicting the inflammatory pathology in the nodal basins. The uptake in the lymph nodes showed complete resolution in the first follow-up study in response to the DMARD therapy [Table 6, Figures 6-9].

## Discussion

RA synovitis is characterized by a massive leukocyte infiltrate, a proliferative synovial membrane, and a neovascularization that gives rise to synovial hypertrophy. An early identification of the pathologic synovitis is of major importance because it represents the primary location of the rheumatoid joint inflammatory process. As metabolic changes support and are likely to precede morphologic changes, molecular imaging techniques that record tissue inflammatory characteristics *in vivo* is of major interest in disease activity assessment. $^{18}$F-FDG PET-CT, due to its ability to image inflammation, theoretically is capable of directly identifying the synovitis and measuring its metabolic activity in inflamed RA joints.

In the present pilot study comparing different response variables (as per ACR-EULAR criteria) and a joint-by-joint imaging analysis, we have shown the feasibility of reliable therapeutic response evaluation in patients of RA to DMARDS with $^{18}$F-FDG-PET-CT.[16] We have been also

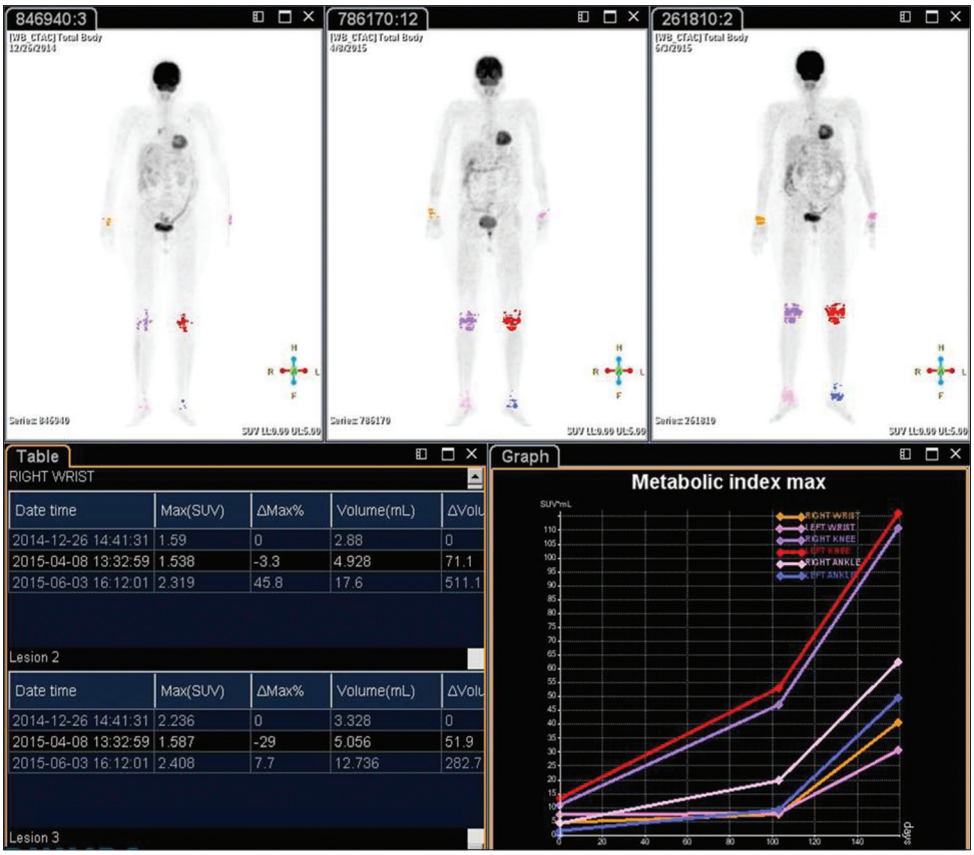


**Figure 9:** Fluoro-2-deoxy-D-glucose-positron emission tomography/computed tomography showing overall no response to both first-line and step-up therapy. The upper three images are maximum intensity projection images showing the joint involvement at baseline, 3, and 6 months. There is an increase in the active inflammation noted in the joints in the first follow-up which is also illustrated by the rise in the curve. This patient was advised etoricoxib, hydroxychloroquine after the baseline scan. After the first follow-up, a step-up therapy was used with addition of methotrexate. The subsequent scan also showed no response with increasing activity. The response is depicted graphically as shown by the rising curves for metabolic volumetric product

able to show that FDG-PET-CT evaluation of synovitis in an individual patient correlates with the classical clinical symptoms, functional, and biologic parameters evaluating RA disease activity. In addition, we also explored and compared the potential of PET-CT over biochemical and EULAR score in assessing the disease treatment response. We found very good intra-and inter-observer agreements for PET-CT identification of synovitis as well as for SUV calculation, confirming the earlier study by Palmer *et al*.

In a previous study by Beckers *et al*., the interobserver variation for SUVs varied with the type of joint analyzed, being best for the knees and ankles and somewhat weaker for the wrists and MCP joints due to the lack of anatomic information on the PET images. This was not observed in the present study due to the availability of additional CT morphological imaging which was an added advantage to precision of our study. The limitations of PET technology in such an application to assessment of joints include a partial-volume effect, which is related to the spatial resolution of the device, leading to an underestimation of the metabolic activity in small structures. This was also significantly improved with better spatial resolution and counting statistics with the employment of modern advanced time of flight-PET-CT scanner used for this study. Furthermore, PET-CT allowed acquisition of the anatomic and metabolic data in the same session, thus facilitating the identification of foci of increased activity and the positioning of the ROIs for quantitative assessment. In another study by the same investigators, Beckers *et al*. demonstrated in 16 rheumatoid knees that the SUVs were significantly correlated with serum CRP levels at baseline; the changes in the SUVs after TNF therapy were also correlated with changes in serum CRP levels.

To the best of our knowledge, therapeutic response assessment in RA using MVP or MTV has been only described by Arisaka *et al*. In their study, interestingly, they described the response assessment in the joints in patients who were using Anti–TNF antibody on PET-CT. In their study, although a correlation existed between SUVs and the volume of the synovitis measured on PET-CT in MVP calculation in all types of joints, the

relationship is stronger with larger joints, such as knees and ankles, than with smaller ones such as MCP and PIP joints.

In recent years, MTV/MVP volumetric measurement of tumor cells with high glycolytic activity has gained a significant importance in oncology, particularly in treatment response evaluation scenario as an adjunct to visual assessment though its use in nononcological conditions is under evaluation. Our study endeavored such individual correlations between the various parameters along with an estimation of Pearson's correlation coefficients with other conventional variables. The results showed a strong correlation of clinical response with MVP response identified on PET-CT scan as early as 3 months. Interestingly, the combined EULAR score change had lesser correlation than that was observed was MVP both at 3 and 6 months.

## Conclusion

The inflammatory activity in the joints of RA can be assessed on $^{18}$F-FDG-PET-CT with semi-quantitative parameters such as SUV and MVP. $^{18}$F-FDG PET-CT results are correlated well with clinical assessment for assessing disease activity and disease response to DMARD therapy in addition to biochemical parameters and EULAR score. MVP as a global metabolic parameter can be utilized for assessing the disease activity and response evaluation on DMARDs. Furthermore, every single joint assessment is possible with PET-CT parameters and SUVmax and MVP estimation, the putative markers of inflammation, which could be generated for each single joint while such assessment is not possible with biochemical parameters. Estimation of imaging response from PET-CT can be a valuable adjunct and help a clinician in deciding upon further management, i.e., continuation of the same drug or use of step-up therapy.

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### Conflicts of interest
There are no conflicts of interest.

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