

# Semi-quantitative analysis of $^{18}\text{F}$ fluorodeoxyglucose uptake in the assessment of disease activity and therapeutic response in rheumatoid arthritis: An institutional experience

## ABSTRACT

$^{18}\text{F}$  fluorodeoxyglucose ( $^{18}\text{F}$ -FDG) positron emission tomography (PET) can be used to image synovial inflammation in patients with rheumatoid arthritis (RA). Recently, clinical application of novel therapies for RA, such as tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) inhibitor and anti-interleukin-6 receptor antibody, has been introduced. The radiological assessment of disease activity changes of patients who underwent these therapies will help the clinicians to obtain more information about the patients and to decide drug withdrawal or change of medication. It is considered that  $^{18}\text{F}$ -FDG PET scan is generally very expensive; however, the information from  $^{18}\text{F}$ -FDG PET about patients during biological treatments helps discontinuation of these treatments with incomplete response despite its high costs and with possible side effects such as malignant lymphoma. In this study, we evaluated if the  $^{18}\text{F}$ -FDG uptake of the affected joints represented by standardized uptake value (SUV) correlated with the clinical assessment of patients with RA. In addition, we would like to evaluate if there was a correlation between the difference of SUV and improvement of clinical findings in RA patients undergoing anti TNF therapies. RA patients who underwent anti-TNF $\alpha$  therapies in a tertiary care hospital were assessed using whole-body  $^{18}\text{F}$ -FDG PET/computed tomography (CT). PET assessments were performed on hip joints, knees, shoulders, wrists, ankles, MCP, and PIP for a total of 28 joints in each patient. The  $^{18}\text{F}$ -FDG uptake was then quantified using the maximum SUV (SUV<sub>max</sub>) prior to, and 6 months after the initiation of treatment with anti-TNF- $\alpha$  drugs. Disease activity score (DAS28 and DAS28-C-reactive protein [CRP]) were recorded and white blood cell, matrix metalloproteinases (MMP-3) and rheumatoid factor (RF) were examined in all patients. The average of SUV<sub>max</sub> among measured joints, or the sum of these joints (total SUV<sub>max</sub>), correlated with DAS28 ( $r = 0.671$ ,  $P < 0.001$ ), DAS28-CRP ( $r = 0.623$ ,  $P < 0.001$ ), ESR ( $r = 0.542$ ,  $P < 0.001$ ), CRP ( $r = 0.411$ ,  $P = 0.002$ ), MMP-3 ( $r = 0.399$ ,  $P = 0.006$ ), and RF ( $r = 0.447$ ,  $P = 0.002$ ). There were correlations between  $\Delta\text{SUV}$  and  $\Delta\text{DAS28}$  ( $r = 0.651$ ,  $P < 0.001$ ),  $\Delta\text{SUV}$  and  $\Delta\text{DAS28-CRP}$  ( $r = 0.682$ ,  $P < 0.001$ ),  $\Delta\text{SUV}$  and  $\Delta\text{ESR}$  ( $r = 0.449$ ,  $P = 0.023$ ), and  $\Delta\text{SUV}$  and  $\Delta\text{MMP-3}$  ( $r = 0.457$ ,  $P = 0.027$ ), respectively. The number of PET-positive joints and the cumulative SUV significantly correlated with the DAS<sub>28</sub>, which is a composite disease activity score (DAS) that combines the swollen and tender joint counts, the erythrocyte sedimentation rate (DAS<sub>28</sub>-ESR) or CRP serum levels (DAS<sub>28</sub>-CRP) or RF (DAS<sub>28</sub>-RF) or metalloproteinases-3 (DAS<sub>28</sub>-MMP-3). At baseline and at 6 months' post-treatment with anti-TNF $\alpha$  drugs, there was a significant correlation between the PET results, either visual, the cumulative SUVs or the composite SUV index, and the comprehensive clinical assessment (DAS<sub>28</sub>), the CRP levels and the number of joints positive for RA, and cumulative synovial thickness. By reflecting inflammatory activity,  $^{18}\text{F}$ -FDG PET may enhance the diagnostic performance and expectation of disease prognosis in RA, especially with early synovial inflammation. The intensity of uptake varied from mild to intense (SUV<sub>max</sub> values from 3.10 to 6.0). Overall, these values correlated well with the clinical evaluation of involved joints.  $^{18}\text{F}$ -FDG PET imaging data provided a distribution of joint involvement with varying degrees of severity and phase of disease activity (moderate, low, and remission) in the same patient. PET/CT imaging with  $^{18}\text{F}$ -FDG shows better image quality, provides more confirmative diagnostic information, and will be promising imaging modality in diagnosis and management of RA.

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## INTRODUCTION

$^{18}\text{F}$  fluorodeoxyglucose ( $^{18}\text{F}$ -FDG) is a glucose analog that is taken up in cells by the glucose transporters on the cell membrane and then phosphorylated to  $^{18}\text{F}$ -FDG-6-phosphate.<sup>[1]</sup> Unlike glucose, it is not further metabolized and trapped in the cytosol. Thus, the amount of intracellular  $^{18}\text{F}$ -FDG-6-phosphate is related to glycolytic activity. Tumor cells overexpress surface glucose transporters and usually have higher glycolytic activity than normal cells leading to increased  $^{18}\text{F}$ -FDG uptake.<sup>[2]</sup>  $^{18}\text{F}$ -FDG can also accumulate in neutrophils, macrophages, and activated lymphocytes. Increased  $^{18}\text{F}$ -FDG uptake in inflammation seems to be associated with several factors: (a) increased number of glucose transporters and an increased expression of the serum glucose transporters by activated inflammatory cells, (b) increased affinity of the glucose transporters for  $^{18}\text{F}$ -FDG in inflammation, probably secondary to the effects of circulating cytokines and growth factors.<sup>[3]</sup>  $^{18}\text{F}$ -FDG competes with glucose, patient preparation generally includes fasting overnight of at least 4–6 h before injection of  $^{18}\text{F}$ -FDG. Positron emission tomography computed tomography (PET/CT) imaging is performed about an hour after injection.

$^{18}\text{F}$ -FDG uptake in the normal bone marrow is low, which may facilitate the distinction of inflammatory cellular infiltrates from normal marrow uptake. Degenerative bone changes usually do not show increased  $^{18}\text{F}$ -FDG uptake.  $^{18}\text{F}$ -FDG uptake normalizes fairly quickly following trauma or surgery, usually within 3–4 months.<sup>[4]</sup>

Rheumatoid arthritis (RA) is a systemic inflammatory autoimmune disorder, which affects both large and small joints. Although heterogeneous, RA is primarily characterized by symmetric, erosive synovitis, which leads to the destruction of cartilage and eventually, underlying bone. In comparison with osteoarthritis (OA), RA typically progresses more rapidly. Radiographs have long been used for the diagnosis of RA but rely on the detection of late stage disease processes such as bone erosions or joint space narrowing. Optimal patient outcomes depend on aggressive treatment with anti-inflammatory drugs early in the disease process. Thus, novel methods to image RA have revolved around early-detection methods and monitoring of treatment response.

## MATERIALS AND METHODS

### Patients

RA patients who underwent anti-tumor necrosis factor- $\alpha$  (anti-TNF $\alpha$ ) therapies in a tertiary care hospital were assessed using whole-body  $^{18}\text{F}$ -FDG PET/CT. Imaging and clinical assessments were performed prior to, and 6 months after the initiation of treatment with anti-TNF- $\alpha$  therapies. DAS28 and DAS28-C-reactive protein (CRP) were recorded and white blood cell (WBC), MMP-3 and rheumatoid factor (RF) were examined in all patients. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Ethics Committee (IEC), and informed consent was obtained from all patients prior to their enrollment in this study (IEC, St. John's Medical College and Hospital; IEC Approval Reference Number: 212/2017; IEC Approval Date: July 6, 2017).

### PET images

The whole-body  $^{18}\text{F}$ -FDG PET was performed following intravenous injection of  $^{18}\text{F}$ -FDG (5 MBq/kg) after fasting for more than 6 h. Data acquisition was done by 3D mode at 60 min using PET-CT machine (Biograph 16, Siemens Medical Solutions Inc.). 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 the reconstruction using an ordered subsets expectation-maximization algorithm into  $128 \times 128$  matrices. PET images were interpreted by experienced physician specializing in nuclear medicine and increased  $^{18}\text{F}$ -FDG uptake in bilateral shoulder, elbow, wrist, hip, knee, ankle joints, MCP, and PIP for a total of 18 joints was recorded.

### Data analysis

For the semi-quantitative analysis, functional images of the standardized uptake value (SUV) were produced using attenuation-corrected transaxial images, injected doses of  $^{18}\text{F}$ -FDG, patient's body weight, and the cross-calibration factor between PET and dose calibrator. SUV was defined as follows:  $\text{SUV} = \text{Radioactive concentration in the region of interest (ROI) (MBq/g)} / \text{Injected dose (MBq)} / \text{Patient's body weight}$ . ROIs were manually drawn at each joint on the SUV images. 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  $^{18}\text{F}$ -FDG uptake. For the assessment of therapeutic response, the difference in mean value of

the maximal SUV of each joints and DAS28 were presented as delta SUV ( $\Delta$ SUV) or delta DAS28 ( $\Delta$ DAS28) for each patient as follows:  $\Delta$ SUV = meanSUVpre-meanSUVpost,  $\Delta$ DAS28 = DAS28pre-DAS28post. MeanSUVpre, meanSUVpost, DAS28pre and DAS28post represent the mean SUV before treatment, the mean SUV after treatment, DAS28 before treatment and DAS28 after treatment, respectively. In addition, in the following result section,  $\Delta$  that placed ahead of each examined items mean the difference of the vale between before and after the treatment. PET assessments were performed on hip joints, knees, shoulders, wrists, ankles, MCP, and PIP for a total of 28 joints in each patient [Table 1]. The 18F-FDG uptake was then quantified using the maximum SUV (SUV<sub>max</sub>). In PET-positive joints according to the visual analysis, the SUV<sub>max</sub> was obtained by drawing a ROI over the most active synovial area identified [Table 1]. When no synovitis was identified, ROIs were placed in the corresponding areas on the CT: At the dorsal surface of the radius (on top of the lunate) for the wrists, over the lateral recess at the level of the midpatella for the knees and for the small joints (MCP, PIP), ROIs were drawn around the appropriate joint. A global metabolic assessment was obtained through the number of PET-positive joints (visual evaluation), the sum of all SUVs (cumulative SUV) and a composite index (CI) taking into account both parameters. The CI is defined as follows: CI = cumulative SUV  $\times$  (number of PET-positive joints/total number of joints evaluated). DAS in 28 Joints-CRP is a scoring system that is widely used to evaluate treatment efficacy and in monitoring disease activity of RA patients in daily practice. It is calculated from 4 parameters: 2 of the parameters are subjective including tender joints (TJs) (range, 0–28) and Patient Global Assessment (range, 0–100), and 2 of them are objective components including swollen joints (range, 0–28) and laboratory value of CRP. It is continuous and ranges from 0.96 to maximum of 9.4 if CRP up to 100 mg/L is considered. A DAS28 value of  $>5.1$  indicates high disease activity. The values of  $3.2 < \text{DAS28} \leq 5.1$  and  $\text{DAS28} \leq 3.2$  are indicative

of moderate and low disease activities, respectively. If DAS28 value is  $<2.6$ , the patients may be considered to be in remission phase.

**Statistics**

Spearman’s rank correlation test was used for the analysis of possible relationships among the different parameters recorded in this study. SPSS v 11.0 software (SPSS Inc., Chicago, IL, USA) was used for the analysis.  $P < 0.05$  was considered statistically significant.

**RESULTS**

Forty-two patients (8 men, 34 women; average age: 52.2 [18–80] years) who underwent anti-TNF $\alpha$  therapies, infliximab (IFX) for 28 patients and etanercept for 14 patients, were assessed. The average disease duration of these patients was 13.4 (1–48) years. The average of meanSUVpre and meanSUVpost was 2.08 (1.11–3.42) and 1.71 (0.99–2.87). DAS28pre, DAS28-CRPpre, DAS28post, and DAS28-CRPpost were 5.22 (3.53–7.41), 4.63 (2.45–6.72), 3.91 (2.45–5.71), and 2.76 (1.32–4.21). The average of SUV<sub>max</sub> among measured joints, or the sum of these joints (total SUV<sub>max</sub>), correlated with DAS28 ( $r = 0.671, P < 0.001$ ), DAS28-CRP ( $r = 0.623, P < 0.001$ ), ESR ( $r = 0.542, P < 0.001$ ), CRP ( $r = 0.411, P = 0.002$ ), MMP-3 ( $r = 0.399, P = 0.006$ ), and RF ( $r = 0.447, P = 0.002$ ). There were correlations between  $\Delta$ SUV and  $\Delta$ DAS28 ( $r = 0.651, P < 0.001$ ),  $\Delta$ SUV and  $\Delta$ DAS28-CRP ( $r = 0.682, P < 0.001$ ),  $\Delta$ SUV and  $\Delta$ ESR ( $r = 0.449, P = 0.023$ ) and  $\Delta$ SUV and  $\Delta$ MMP-3 ( $r = 0.457, P = 0.027$ ), respectively.  $\Delta$ WBC was not significantly correlated with the  $\Delta$ SUV ( $r = 0.269, P = 0.230$ ), and  $\Delta$ CRP with  $\Delta$ SUV ( $r = 0.287, P = 0.217$ ). The number of PET-positive joints and the cumulative SUV significantly correlated with the DAS<sub>28</sub>, which is a composite DAS that combines the swollen and TJ counts, the erythrocyte sedimentation rate (DAS<sub>28</sub>-ESR) or CRP serum levels (DAS<sub>28</sub>-CRP) or RF (DAS<sub>28</sub>-RF) or DAS<sub>28</sub>-MMP-3. There was correlation between  $\Delta$ SUV and  $\Delta$ DAS<sub>28</sub> values measured after 6-month treatment with anti-TNF- $\alpha$  drugs. We used the clinical response according to the EULAR criteria as the gold standard against which the imaging and biological parameters were confronted. The clinical response was defined at 3 and 6 months post treatment. According to these criteria, a good response was defined as a significant decrease in DAS<sub>28</sub> ( $>1.2$ ) and a low level of disease activity ( $\leq 3.2$ ). Non-response was defined as a decrease  $\leq 0.6$ , or a decrease  $>0.6$  and  $\leq 1.2$  with an attained DAS<sub>28</sub>  $>5.1$ . Any other scores were regarded as moderate responses. At 3 months, moderate responses were observed in 28 patients and no response in 14 patients. At 6 months, moderate responses were observed in 38 patients

**Table 1: Correlation between visual analysis and positron emission tomography/computed tomography results at baseline and at 6 months’ post-treatment with antitumor necrosis factor  $\alpha$  drugs**

| Joints | Baseline        |      | 6 months’ post-treatment with anti-TNF $\alpha$ drugs |      |
|--------|-----------------|------|---|------|
|        | Visual analysis | SUVs | Visual analysis                                       | SUVs |
| Knees  | 0.73            | 0.93 | 0.83  | 0.90 |
| Wrists | 0.71            | 0.78 | 0.73  | 0.91 |
| MCPs   | 0.75            | 0.95 | 0.67  | 0.84 |
| PIPs   | 0.78            | 0.97 | 0.62  | 0.95 |
| Global | 0.77            | 0.91 | 0.68  | 0.91 |

TNF $\alpha$ : Tumor necrosis factor  $\alpha$ ; SUVs: Standardized uptake values; MCPs: Metacarpophalangeals; PIPs: Proximal interphalangeals

and no response in 4 patients. The images were first visually analyzed and joints were considered as positive for synovitis when the  $^{18}\text{F}$ -FDG uptake was increased compared to the background in areas corresponded to joint synovium on CT, i.e., either when thickened synovium was recognized on CT or in locations corresponding anatomically to synovium, excluding uptake in other structures such as muscle and tendons. The  $^{18}\text{F}$ -FDG uptake was then quantified using the maximum  $\text{SUV}_{\text{max}}$ . In PET-positive joints according to the visual analysis, the  $\text{SUV}_{\text{max}}$  was obtained by drawing a ROI over the most active synovial area identified. At baseline however, there was a significant correlation between the PET results, either visual, the cumulative SUVs or the composite SUV index on the one hand, and the comprehensive clinical assessment ( $\text{DAS}_{28}$ ), the CRP levels and the number of joints positive for RA, and cumulative synovial thickness [Table 2]. There was significantly correlation between  $\Delta\text{SUV}$  and  $\Delta\text{DAS}_{28}$  results at 6 months' post-treatment [Table 2].

## DISCUSSION

As inflammation is a key component to RA pathogenesis,  $^{18}\text{F}$ -FDG PET is a logical molecular imaging marker to study the disease.<sup>[5]</sup> In fact,  $^{18}\text{F}$ -FDG has been applied to studying RA in all segments of the disease cycle. Strong correlations have been cited between PET observations (e.g., number of PET-positive joints and cumulative SUV) and underlying disease activity.<sup>[6]</sup> Further, it has been shown that early changes in regional  $^{18}\text{F}$ -FDG uptake in RA patients undergoing anti-TNF- $\alpha$  (IFX) treatment were related to global disease activity in later clinical assessment.

In recent years,  $^{18}\text{F}$ -FDG PET can be used to image inflammation in patients with arthritis.  $^{18}\text{F}$ -FDG PET imaging has been used to assess the metabolic activity of synovitis in patients with RA and to evaluate the disease activity of RA. Several reports indicated that there was a significant correlation between the visual assessment of  $^{18}\text{F}$ -FDG uptake, i.e., visual uptake score and clinical evaluation of disease activity.<sup>[7]</sup> Furthermore, PET findings have been correlated with magnetic resonance imaging (MRI) and ultrasonography (US) assessments of the

pannus in patients with RA as well as with the classical serum parameter of inflammation, CRP and MMP-3.

Recent advancement in the medical biology and pharmaceutical engineering allows the use of new drugs such as TNF- $\alpha$  inhibitor, anti-interleukin-6 receptor antibody. The clinical application of novel therapy for RA has stimulated increased interest in the radiological assessment of disease activity. One of the merits of PET is quantitative measure of metabolic activity. A few studies have been performed to examine the possible role of  $^{18}\text{F}$ -FDG PET to see the disease activity of RA.<sup>[6]</sup> Previous studies have evaluated  $^{18}\text{F}$ -FDG joint uptakes based on visual assessment score, i.e., visual uptake score.<sup>[8]</sup> Hence, in this study, we evaluated if the  $^{18}\text{F}$ -FDG uptake of the affected joints represented by SUV correlated with the clinical assessment of patients with RA. In addition, we would like to evaluate if there was a correlation between the difference of SUV and improvement of clinical findings in RA patients undergoing anti-TNF therapies.

Goerres *et al.*<sup>[9]</sup> assessed seven RA patients prior to, and 12 weeks after IFX treatment using  $^{18}\text{F}$ -FDG PET total joint score and concluded that visual assessment of  $^{18}\text{F}$ -FDG uptake showed a significant correlation with clinical evaluation of disease activity in patients undergoing anti-inflammatory treatment. Kubota *et al.*<sup>[10]</sup> demonstrated the visual  $^{18}\text{F}$ -FDG uptake score might be useful for evaluating arthritis in large joints. They studied the total  $^{18}\text{F}$ -FDG score was significantly correlated with the CRP level, however, the total  $\text{SUV}_{\text{max}}$  and the CRP level were weakly, but not significantly, correlated.

In this study, for the semi-quantitative analysis and focusing on the utility in clinical practice, we used  $\text{SUV}_{\text{max}}$  for the grade of  $^{18}\text{F}$ -FDG uptake. There were the correlations between total  $\text{SUV}_{\text{max}}$  and clinical findings ( $\text{DAS}_{28}$ ,  $\text{DAS}_{28}$ -CRP, ESR, CRP, MMP-3, and RF). The difference of the mean  $\text{SUV}_{\text{max}}$  between before and after anti-TNF- $\alpha$  therapies was significantly correlated with the difference of  $\text{DAS}_{28}$  and  $\text{DAS}_{28}$ -CRP, respectively.

One limitation with  $^{18}\text{F}$ -FDG PET is that the tracer detects glucose metabolism but may not be specific to inflammation.

**Table 2: Correlation between the positron emission tomography/computed tomography results (number of positron emission tomography-positive joints, cumulative standardized uptake value index) and the biological, clinical and US parameters, at baseline and at 6 months' post-treatment with antitumor necrosis factor  $\alpha$  drugs**

| Joints                             | Baseline       |                | 6 months post-treatment with anti-TNF $\alpha$ drugs |                |
|------------------------------------|----------------|----------------|--|----------------|
|                                    | PET (+) joints | Cumulative SUV | PET (+) joints                                       | Cumulative SUV |
| CRP                                | 0.59*          | 0.5*           | 0.37*  | 0.52*          |
| $\text{DAS}_{28}$                  | 0.68*          | 0.69*          | 0.12*  | 0.22*          |
| US (# positive joints)             | 0.73*          | 0.67*          | 0.53*  | 0.55*          |
| Cumulative synovial thickness (mm) | 0.65*          | 0.74*          | 0.83*  | 0.64*          |

\* $P < 0.05$ . CRP: C-reactive protein; #stands for "Number";  $\text{DAS}_{28}$ : Disease activity score 28; PET: Positron emission tomography; TNF $\alpha$ : Tumor necrosis factor  $\alpha$ ; SUV: Standardized uptake value; US: Ultrasonography

Alternatively, other PET radiotracers can track different processes such as cellular proliferation (i.e., by <sup>11</sup>C-Choline). The previous work has evaluated PET scans with <sup>11</sup>C-Choline and <sup>18</sup>F-FDG in relation to synovial volume to characterize RA changes.<sup>[11]</sup> A direct marker of inflammation, such as <sup>11</sup>C-®-PK11195 that tags macrophages in the inflammatory pathway, may offer more specific molecular targets to study RA.<sup>[12,13]</sup>

MRI has similarly been developed for early detection of RA and to assess disease severity. Unlike PET, MRI provides high-resolution anatomical images to assess structural changes (e.g., peri-articular erosions, BMLs, and synovial thickening) for diagnosis and staging of RA disease.<sup>[14]</sup> Contrast enhancement following injection of gadolinium can further differentiate active inflammation from synovitis. Compared with radiographs, MRI offers tomographic information of various contrast methods to provide better visualization and differentiation of soft tissue. Further, MRI's advanced capabilities for early identification of bone erosions are important considerations for choice of treatment.<sup>[15]</sup> For patients undergoing treatment, scoring systems that evaluate the features of RA from MRI show great potential for monitoring response to therapy. Finally, new MRI methods, such measurement of apparent diffusion coefficient and pharmacokinetic modeling of gadolinium enhancement and washout, offer quantitative metrics to more precisely study RA pathogenesis.<sup>[16]</sup>

Hybrid PET imaging offers the potential to enhance the utility of nuclear medicine techniques to study RA. Studies with PET/CT have shown the importance of <sup>18</sup>F-FDG uptake in differentiating enteropathies from synovitis in RA conditions.<sup>[12]</sup> The use of <sup>18</sup>F-FDG reveals clinical inflammation in a majority of RA-affected joints and with greater <sup>18</sup>F-FDG uptake than comparable OA regions.<sup>[17]</sup> Hybrid PET-MRI systems additionally offer high-resolution morphologic images and multiple contrasts in soft tissue to enhance the study of RA. In a recent study, true hybrid PET/MRI was performed in early hand RA; <sup>18</sup>F-FDG uptake corresponded to sites of synovitis and tenovaginitis as identified on contrast-enhanced MRI, demonstrating the feasibility of PET-MRI to image inflammation in RA.<sup>[18]</sup>

## CONCLUSION

By reflecting inflammatory activity, <sup>18</sup>F-FDG PET may enhance the diagnostic performance and expectation of disease prognosis in RA, especially with early synovial inflammation. The intensity of uptake varied from mild to intense (SUV<sub>max</sub> values from 3.10 to 6.0). Overall, these values correlated

well with the clinical evaluation of involved joints. <sup>18</sup>F-FDG PET imaging data provided a distribution of joint involvement with varying degrees of severity and phase of disease activity (moderate, low, remission) in the same patient. PET/CT imaging with <sup>18</sup>F-FDG shows better image quality, provides more confirmative diagnostic information, and will be promising imaging modality in diagnosis and management of RA.

## Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

## Conflicts of interest

There are no conflicts of interest.

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