Title: Role of technetium-99m methylene diphosphonate SPECT/CT in the detection of sacroiliitis in patients with spondyloarthritis - comparison with clinical markers and MRI.

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Short Running Title: SPECT/CT versus MRI in the diagnosis of spondyloarthritis
Abstract

**Rationale:** To evaluate the role of $^{99m}$Tc-MDP SPECT/CT for the detection of sacroiliitis in spondyloarthopathies (SpA) and comparison with clinical markers and MRI. **Methods:** A total of 155 diagnosed patients (83M : 72 F; mean age 35.80±12.40 years; range 18-60 years ) with SpA as per the European Spondyloarthropathy Study Group criteria (ESSG) criteria were prospectively included. All the patients were subjected to clinical evaluation (using BASDAI scoring), ESR, CRP levels, planar $^{99m}$Tc MDP bone scintigraphy, hybrid SPECT/CT and MRI of the pelvic region. Using MRI as the reference criterion, diagnostic accuracy of clinical and scintigraphic parameters was assessed. On planar bone scintigraphy/SPECT, score of 0, 1, 2 was assigned when the tracer uptake in the SI joint was less than, equal to and more than the sacrum. A score of ‘2’ was considered as positive for the diagnosis of sacroiliitis. **Results:** Using MRI as the reference standard, sensitivity, specificity, accuracy, positive predictive value and negative predictive value of $^{99m}$Tc MDP SPECT/CT were 90.0%, 80.0%, 87.0%, 92.0%, and 75.0% respectively. The accuracy of SPECT/CT (87%) was better than ESR (58.1%), CRP (32.9%), BASDAI scoring (77%) and planar bone scintigraphy (53%). Similar results were found for sensitivity and negative predictive values. Specificity of SPECT/CT (80%) was lower than BASDAI scoring (88.6%) and equal to planar bone scintigraphy (80%). Positive predictive value of SPECT/CT (92%) was bit lower than BASDAI scoring (93.6%). Kappa values for planar $^{99m}$Tc MDP bone scan and hybrid SPECT/CT were 0.167 and 0.673 indicating poor agreement for planar bone scan and good agreement for hybrid SPECT/CT images respectively. A significant (p <0.001) correlation (r= 0.659) was observed between SPECT/CT and MRI findings. **Conclusion:** $^{99m}$Tc-MDP SPECT/CT imaging has diagnostic accuracy comparable to MRI for the evaluation of sacroiliitis in SpA and can thus be used as an alternative to MRI in cases having contraindications to the use of MRI. SPECT/CT shows better accuracy than planar bone scintigraphy, ESR, CRP and BASDAI scoring in diagnosis of sacroiliitis.

**Keywords:** $^{99m}$Tc-MDP, SPECT/CT, sacroiliitis, spondyloarthopathies, MRI, clinical markers
Introduction

Spondyloarthropathies (SpA) are characterized by seronegative and inflammatory arthritis generally involving the spine and presenting clinically as peripheral arthritis and enthesitis. The spectrum of SpA includes ankylosing spondylitis (AS), psoriatic arthritis (PsA), enteropathtic SpA (EnSpA), reactive arthritis (ReA) and undifferentiated spondyloarthritis (uSpA). The prevalence of SpA in India is estimated to be between 0.1% - 0.4% and that of AS about 0.2% (1-4). Ankylosing spondylitis, the prototype of SpA, is one of the most common inflammatory rheumatic diseases (5, 6). In early AS and uSpA, sacroiliitis is an early clinical finding and is generally presumed as the first manifestation of the disease (7). The current criteria for classification of SpA are the European Spondyloarthropathy Study Group criteria (ESSG) and Amor criteria for the classification of AS are the modified New York criteria (8-10).

The disease classification based upon the AS criteria depends on radiological evidence of sacroiliitis. These criteria do not cover the early AS phase due to lack of radiological evidence, which often presents late in the disease. This may cause a delay both in establishing the final diagnosis as well as in initiating early and appropriate treatment in AS patients (11). The diagnosis of sacroiliitis using more sensitive modalities like magnetic resonance imaging (MRI) may reduce the time required for arriving at a final diagnosis either of AS or SpA (12,13). MRI is known to have higher sensitivity than plain radiography and other imaging modalities in detecting sacroiliitis (14-16). However, because of some inherent technical limitations and contraindications, it is not always possible to use MRI in the routine diagnosis of sacroiliitis (17).

Planar $^{99m}$Tc-MDP bone scintigraphy has been extensively used in diagnosis of sacroiliitis (14, 15). A hybrid SPECT/CT imaging allows three-dimensional localization of tracer activity to the sacroiliac joints. Limited studies in small patients’ number have shown that SPECT/CT bone imaging may be a useful modality to identify sacroiliitis in SpA patients and thus may provide an alternative to MRI (18, 19, 20). In the present study, we compared the diagnostic utility of hybrid SPECT/CT imaging with MRI for the detection of sacroiliitis in SpA in a larger cohort.
Methods

A total of 155 consecutively diagnosed patients of SpA (83 male, 72 female) aged 18-60 (mean 35.8±12.40) years were prospectively included in the study. The study was approved by the ethics committee of the institute. All the patients recruited in the study met the European Spondyloarthropathy Study Group (ESSG) criteria having characteristic clinical symptoms of insidious onset of inflammatory back pain, duration more than three months and morning stiffness improving subsequently on exercise. Patients who had radiographic evidence of grade 2 sacroiliitis; history of brucella, tuberculosis, septic sacroiliitis, endocrine/metabolic diseases, any malignancy and pregnant patients were excluded from the study. Each patient was subjected to a functional clinical examination using BASDAI scoring, ESR and CRP levels. All the patients underwent technetium-99m methylene diphosphonate (99mTc-MDP) bone scintigraphy, hybrid SPECT/CT imaging and MRI of sacroiliac (SI) joints.

99mTc-MDP bone scanning (Planar and SPECT/CT)

Following an intravenous injection of approximately 740.0 MBq of freshly prepared 99mTc-MDP, anterior and posterior whole body images were acquired at 3 hours post-injection. The image acquisition was done in 256x1024 matrix at a scan speed of 14 cm/min. Bone scanning in each patient was performed using a double head hybrid (SPECT/CT) gamma camera equipped with a low-energy, high-resolution collimator (Infinia Hawkeye 4, GE healthcare, Milwaukee, USA).

Immediately after the completion of the whole body image acquisition, SPECT images of the pelvic region were acquired in a 64 × 64 matrix, using the step-and-shoot method covering a 360° circular orbit in 60 projections (30 sec/projection). Following the SPECT acquisition, a non diagnostic CT scan of the pelvic region was also acquired in helical mode with a tube current of 2.5 mA. The SPECT/CT data were reconstructed using an iterative reconstruction algorithm (OSEM; 2 iterations: 10 subsets) by applying Hann filter (cut-off frequency 0.9) using Volumetrix Protocol on Xeleris TM 2 workstation (version 2006). Subsequently, the reconstructed data were displayed for visual interpretation of the tracer uptake in the region of sacroiliac (SI) joints.
For the visual scoring, a score of ‘0’ was assigned when the tracer uptake in the SI joint was less than sacrum; a score of ‘1’ when the activity in the SI joint was equal to sacrum and a score of ‘2’ when the tracer concentration in the SI joint was more than sacrum. A score of ‘2’ was considered as positive for the diagnosis of sacroiliitis on the planar bone scan and hybrid SPECT/CT images. Planar bone scintigraphy and SPECT images were reviewed independently and scoring done by 2 experienced nuclear physicians. In cases in which discrepancy was there, consensus was reached by discussion. A comparative analysis was performed between the planar and hybrid SPECT/CT techniques for the accurate detection of sacroiliitis in SpA by considering the MRI findings as the criterion standard.

**Magnetic resonance imaging (MRI)**

MRI was performed using 3.0 Tesla (Siemens, Verio) or 1.5 Tesla (Siemens, Aera) whole body MR units equipped with standard head coil. The axial images had a FOV of 350 mm with a 4 mm slice thickness to see the whole paravertebral area. The axial and coronal T1-weighted images (TR, 600 ms; TE, 15 ms) were acquired after Gadolinium-DTPA (0.05 mole per kg) contrast administration. A matrix of 224 x 256 was used for the axial images. MRI findings were analyzed independently by an experienced radiologist. The sacroiliitis was diagnosed, if MR imaging showed any one of the following features (a) a loss of normal uniform cartilage signal intensity (b) bone marrow edema and synovial enhancement and (c) an increase in signal intensity in the joint, erosions, sclerosis and ankylosis (chronic sacroiliitis).

**Clinical Markers**

ESR (Westergren) and CRP (ELISA with ELISA plate reader) levels were used to assess inflammation. Biochemical evidence of disease activity was defined by the presence of high ESR (>20 mm/h; normal range 0–20 mm/h) and CRP (>5 mg/L; normal range 0–5 mg/L) levels. Patients answered questionnaires for assessment of symptoms of sacroiliitis based upon BASDAI scoring.

Using this scoring criteria, a score of ≤ 3.9 denotes no active disease, a score between 4 and 6.9 denotes that the disease activity was ambiguous and a score of ≥7.0 denotes a definitive disease activity.
The three imaging procedures were performed within two weeks after the clinical assessment. All the patients gave written and informed consent for their participation in the study.

**Statistical analysis**

Statistical analysis was done using SPSS software for Windows (Version 17.0; SPSS, Inc., Chicago, IL, USA). Data was represented in the form of tables and bar diagram. Sensitivity, specificity, accuracy, positive predictive value (PPV) and negative predictive value (NPV) were calculated using MRI as the “reference standard”. The agreement between planar $^{99m}$Tc-MDP bone scan, hybrid SPECT/CT and MRI was tested by using kappa statistics. Correlation of MRI was done with inflammatory markers (ESR, CRP) and functional assessment of the disease activity by BASDAI criteria. Kappa values lower than 0.4, between 0.4 and 0.75, and greater than 0.75 were considered to represent poor, fair to good and excellent agreements respectively. Statistical significance for all analyses was assessed at $p < 0.05$.

**Results**

The demographic details of the patients i.e. age, disease duration, pain scoring (based on BASDAI criteria) and the results of the laboratory investigations (ESR and CRP) are presented in Table-1. The results are presented as mean, median and range values. The mean age was $35.8 \pm 12.4$ years and the mean disease duration was $14.2 \pm 19.5$ months. The mean ESR (mm/h) and CRP values were $26.6 \pm 17.5$ and $15.3 \pm 10.2$ respectively. The mean scores of BASDAI criteria were $2.9 \pm 1.9$.

In the present study, we found that $62.0\%$ (95/155) of the patients were found to have AS, $33.0\%$ (50/155) had uSpA and $3.8\%$ (7/155) had ReA. The remaining $1.2\%$ (3/155) of the patients had PsA. One hundred and four patients out of 155 were found to have HLA-B27 positive results. MRI findings were positive for sacroiliitis in 111 and negative in 44 patients. The findings were suggestive of acute/active sacroiliitis in 83 (20 unilateral, 63 bilateral) and chronic sacroiliitis in 28 patients respectively. Planar $^{99m}$Tc-MDP bone scan findings were positive for sacroiliitis in 54 and negative in 101 patients respectively. On the other hand, hybrid SPECT/CT findings were positive for sacroiliitis in 108 and negative in 47 patients respectively.
Figure-1 shows negative findings for sacroiliitis on planar bone scan (A), SPECT/CT (B) and MRI (C) scanning with score of ‘1’ each on both planar (anterior and posterior images) and SPECT/CT. Figure-2 presents positive findings for bilateral sacroiliitis on SPECT/CT (B) and MRI (C), with score of ‘2’ on SPECT/CT due to accurate localization of tracer activity in the sacrum and SI joints whereas the planar bone scan (A) showing equal tracer uptake in the sacrum and SI joints.

The comparative diagnostic utility of the clinical markers and imaging techniques used in the present study is presented in Table-2. Planar $^{99m}$Tc-MDP bone scanning demonstrated low sensitivity (42.0%), accuracy (53.0%) and NPV (36.0%) for the diagnosis of sacroiliitis. In comparison, hybrid SPECT/CT offered higher values of 90.0%, 87.0% and 75.0% for sensitivity, accuracy and NPV respectively. Likewise, the PPV for hybrid SPECT/CT results was higher (92.0%) than that of the planar bone scanning (85.0%). The two techniques however, demonstrated similar specificity of 80.0%.

Agreement between each of the different modalities with the reference standard ‘MRI’ was done using kappa statistics. Kappa values for planar $^{99m}$Tc-MDP bone scan and hybrid SPECT/CT were 0.167 and 0.673 indicating poor agreement for planar bone scan and good agreement for hybrid SPECT/CT images respectively. Pearson correlation co-efficient analysis demonstrated good correlation ($r = 0.659; p< 0.001$) between SPECT/CT and MRI findings. The accuracy of SPECT/CT (87%) was better than ESR (58.1%), CRP (32.9%), BASDAI scoring (77%) and planar bone scintigraphy (53%). Similar results were found for sensitivity and negative predictive value. Specificity of SPECT/CT (80%) was lower than BASDAI scoring (88.6%) and equal to planar bone scintigraphy (80%). Positive predictive value of SPECT/CT (92%) was bit lower than BASDAI scoring (93.6%)

**Discussion**

Inflammatory involvement of the sacroiliac joints is an important criterion for establishing the diagnosis of SpA (7), which occurs most commonly in young patients. An early diagnosis is critical for initiation of appropriate treatment as well as for the productive life span of these patients. Plain radiography has always been a part of the diagnostic work-up and the classification criteria for SpA. However, radiographic evidence of sacroiliitis usually becomes
apparent only after a few years after the symptomatic onset of the disease (11). MRI has been found to be superior to other imaging techniques for the accurate detection of early change in cartilage/bony erosions (19-20). MRI is contraindicated in patients with claustrophobia, pacemakers and metal implants. These patients may require an alternative imaging technique for the diagnosis of sacroiliitis.

In the present study, we found that the BASDAI test demonstrated low sensitivity (69.4%) and accuracy (77.0%) for the detection of sacroiliitis. These results are in concordance with those of the previous investigators, who found no significant association between MRI findings and BASDAI results (21). Likewise, we observed that the levels of acute phase reactants (ESR and CRP) also exhibited low sensitivity and accuracy. These values were 52.0%; 58.1% and 17.1%; 32.9% for ESR and CRP respectively. The role of ESR and CRP in the diagnosis of sacroiliitis remains controversial (22). An inter-observer variations in grading sacroiliac radiographs have been reported (23, 24).

Many previous studies have compared the diagnostic utility of planar/SPECT bone scanning with plain radiography, CT and MRI. However, to the best of our knowledge, evaluation of the role of hybrid imaging (SPECT/CT) and comparison with MRI has not been reported previously. In this study, we present the initial results on the comparison of clinical markers, planar, hybrid SPECT/CT bone scanning and MRI for the diagnosis of sacroiliitis in a cohort of 155 patients having SpA. A low dose non diagnostic CT done as part of SPECT/CT was used for localization of the tracer activity only. Statistical analysis of the scan results show that SPECT/CT has higher sensitivity, diagnostic accuracy and positive predictive value than planar bone scanning.

It has been reported previously that pooled sensitivity of the planar bone scan while comparing the results with the reference standard ‘MRI’ to detect sacroiliitis in AS was 59.5% (25, 26). Contrast enhanced MRI has been reported to be superior to quantitative SI scintigraphy or conventional radiography in detecting early SI. However, its specificity is limited by previous inflammatory episodes (27). The observed variation in the sensitivity of planar bone scans for detecting sacroiliitis is attributed to factors like gender, ethnicity, past history of drug therapy, imaging time, urinary bladder activity, past history of trauma or fracture of bone, patients’ movement, injection site and different ROI selection in quantitative study
In the present study, we found that planar bone scanning had sensitivity of only 42.0%, compared to 90.0% for hybrid SPECT/CT.

Henly et al observed that $^{99m}$Tc-MDP SPECT exhibited higher sensitivity than planar scintigraphy and subsequently reported that MRI was the most sensitive and SPECT the most specific technique for the detection of sacroiliitis (29-30). It was highlighted by these authors that SPECT alone does not identify the cause of inflammatory disease and the characteristics of sacroiliitis. Therefore, hybrid SPECT/CT of the pelvic region may overcome the technical limitations of both planar bone scintigraphy and SPECT alone in the evaluation of sacroiliitis. The use of SPECT of the pelvic region provides three-dimensional imaging of the distribution of radioactivity in and around the SI joint. The fused hybrid SPECT/CT image helps in the identification of tracer localization in the sacrum and iliac bones forming the SI joint (Figure - 2B). If diagnostic CT is done as a part of the hybrid SPECT/CT, erosions and subchondral sclerosis, joint space alteration and new bone formation can be noted, which can play a complimentary role in making the final diagnosis of sacroiliitis.

In the present study, hybrid SPECT/CT imaging significantly improved the sensitivity of planar bone scanning in the detection of sacroiliitis in SpA. Combining $^{99m}$Tc-MDP bone scan with hybrid SPECT/CT, sacroiliitis can be accurately detected in seronegative SpA patients and has diagnostic accuracy comparable with MRI taking as criterion standard.

**Limitations**

Non diagnostic CT was done as a part of SPECT/CT study to localize the tracer activity. Incremental value of CT changes was not evaluated separately, which may lead to higher accuracy of hybrid SPECT/CT.

**Conclusions:** $^{99m}$Tc-MDP SPECT/CT imaging has diagnostic accuracy comparable to MRI for the evaluation of sacroiliitis in SpA and can be used as an alternative to MRI in cases having contraindications to the use of MRI. SPECT/CT shows better accuracy than planar bone scintigraphy, ESR, CRP and BASDAI scoring in diagnosis of sacroiliitis.
References:


Figure 1:

Anterior and posterior whole body planar Tc-99m MDP bone scan images (A) in a 25 years old male patient with history of lower backache for 6 months demonstrating equal tracer uptake (arrows) in the sacrum and SI joints; hybrid SPECT/CT of the pelvic region (B) showing equal tracer uptake (arrows) in the sacrum and SI joints with no abnormal CT finding (arrow). MRI images of bilateral SI joints (C) also show no abnormal feature of sacroiliitis. All the three imaging modalities showing no features of sacroiliitis.
Anterior and posterior whole body planar Tc-99m MDP bone scan images (A) in a 47 years-old male AS patient with history of lower backache for 10 months indicating symmetrical tracer uptake (arrows) in the sacrum and SI joints (negative for sacroiliitis). A hybrid SPECT/CT (B) showing increased tracer uptake (arrows) localized in and around both SI joints as compared to the sacrum (suggestive of bilateral sacroiliitis) similar to the MRI findings (C) showing bilateral sacroiliitis (arrows). Both hybrid SPECT/CT and MRI images showing features of bilateral sacroiliitis with normal planar bone scan.
Table 1 Clinical and laboratory findings of the patients

<table>
<thead>
<tr>
<th>Profiles</th>
<th>Mean ±SD</th>
<th>Median</th>
<th>Min- Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age(years)</td>
<td>35.8±12.40</td>
<td>35.0</td>
<td>18-60</td>
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<tr>
<td>Duration(months)</td>
<td>14.22±19.5</td>
<td>6.0</td>
<td>3-96</td>
</tr>
<tr>
<td>*ESR(mm/h)</td>
<td>26.61±17.49</td>
<td>20.0</td>
<td>8-113</td>
</tr>
<tr>
<td>**CRP(mg/L)</td>
<td>15.34±10.23</td>
<td>8.0</td>
<td>2-25</td>
</tr>
<tr>
<td>***BASDAI</td>
<td>2.9±1.89</td>
<td>3.0</td>
<td>1-9</td>
</tr>
</tbody>
</table>

*ESR: erythrocyte sedimentation rate, **CRP: C reactive protein, ***BASDAI: Bath Ankylosing Spondylitis Disease Activity Index
Table 2 The sensitivity, specificity, accuracy, positive and negative predictive values of different modalities, using MRI as the “Reference Standard”

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Accuracy (%)</th>
<th>Positive predictive Value (%)</th>
<th>Negative predictive Value (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>*ESR</td>
<td>52%</td>
<td>56.8%</td>
<td>58.1%</td>
<td>75.3%</td>
<td>32.1%</td>
</tr>
<tr>
<td>**CRP</td>
<td>17.1%</td>
<td>72.7%</td>
<td>32.9%</td>
<td>61.3%</td>
<td>25.8%</td>
</tr>
<tr>
<td>***BASDAI</td>
<td>69.4%</td>
<td>88.6%</td>
<td>77%</td>
<td>93.6%</td>
<td>53.4%</td>
</tr>
<tr>
<td>Planar 99mTc MDP bone scan</td>
<td>42%</td>
<td>80%</td>
<td>53%</td>
<td>85%</td>
<td>36%</td>
</tr>
<tr>
<td>Hybrid SPECT/CT</td>
<td>90%</td>
<td>80%</td>
<td>87%</td>
<td>92%</td>
<td>75%</td>
</tr>
</tbody>
</table>

*ESR: erythrocyte sedimentation rate, **CRP: C reactive protein, ***BASDAI: Bath Ankylosing Spondylitis Disease Activity Index