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ORIGINAL ARTICLE

Synovitis and bone inflammation in early rheumatoid arthritis: high-resolution multi-pinhole SPECT versus MRI

Christian Buchbender, Benedikt Ostendorf, Katalin Mattes-György, Falk Miese, Hans-Joerg Wittsack, Michael Quentin, Christof Specker, Matthias Schneider, Gerald Antoch, Hans-Wilhelm Müller, Axel Scherer

PURPOSE

We aimed to assess the relationship between bone inflammation in multi-pinhole single-photon emission computed tomography (MPH-SPECT) and synovitis detected by magnetic resonance imaging (MRI) in early rheumatoid arthritis patients.

MATERIALS AND METHODS

MPH-SPECT with technetium dicarboxypropanedisphosphonate (Tc-99mDPD) and 3 Tesla MRI were performed in 10 early rheumatoid arthritis patients. Eighty finger joint sites were assessed for increased osteoblastic activity using visual and region-of-interest (ROI) analysis. Presence of joint inflammation in MRI was investigated using the subscores of the rheumatoid arthritis MRI score.

RESULTS

Tc-99mDPD uptake was increased in 38 (47.5%) and 22 (27.5%) joint sites as determined by visual and ROI analysis, respectively. A total of 32 (84.2%) sites with increased bone metabolism showed a normal MRI bone signal. The MPH-SPECT uptake ratio was elevated only in the subgroup with severe synovitis (P < 0.001).

CONCLUSION

In early rheumatoid arthritis, molecular imaging with MPH-SPECT detects higher rates of inflammatory bone involvement compared to MRI. Our preliminary data suggest that osteitis is related to severe synovitis.

From the Departments of Diagnostic and Interventional Radiology (C.B., F.M., H.W., M.Q., G.A., A.S.), Rheumatology (B.O. \boxtimes *ostendorf@med.uni-duesseldorf.de*, M.S.), and Nuclear Medicine (K.M., H.M.), Univ Dusseldorf, Medical Faculty, Dusseldorf, Germany; the Department of Rheumatology & Clinical Immunology (C.S.), Kliniken Essen-Sued, Essen, Germany.

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Published online 13 December 2012 DOI 10.4261/1305-3825.DIR.5922-12.1 R heumatoid arthritis (RA), the most common inflammatory rheumatic disease, may lead to severe joint destruction and disability (1). While the potential involvement of cartilage and bone in RA is undisputed, the corresponding pathogenesis is subject to ongoing discussion. The traditional concept of inflammatory pannus, in which fibroblast-like synoviocytes provoke cartilage and bone destruction through direct invasion and trigger of catabolic cascades, has been termed the outside-in hypothesis (2, 3). There is also evidence supporting an osteitis-centered approach, referred to as the inside-out hypothesis, in which joint inflammation originates from the bone marrow (2, 3).

Magnetic resonance imaging (MRI) is sensitive to inflammatory changes of the synovium (4). Bone marrow edema representing osteitis (5) is detectable by fluid-sensitive MRI techniques (6). Thus, MRI may depict imaging features of both pathogenetical hypotheses mentioned above.

Bone osteoblastic activity is typically evaluated through technetium dicarboxypropanedisphosphonate (Tc-99mDPD), preferably via single-photon emission computed tomography (SPECT) if sensitive detection is required (7). Increased osteoblast activity has been found to account for a main component of Tc-99mDPD uptake into inflamed bone (8). Multi-pinhole SPECT (MPH-SPECT), which was developed and evaluated for small animal research (9, 10), has been shown to yield high-resolution data in small joints (11). In humans, MPH-SPECT allows for depictions of very initial bony alterations in early RA that are not detectable on MRI scans (12–14).

The purpose of this study was to systematically assess the relationship between bone inflammation in MPH-SPECT and synovitis detected by MRI in early RA patients.

Materials and methods

Patients

The study was approved by the institutional review board. Informed consent was obtained from all subjects. Inclusion criteria were diagnosis of early RA based on the 2010 American College of Rheumatology/ European League Against Rheumatism RA classification criteria (15), disease duration longer than 6 months, and no previous therapy with disease-modifying anti rheumatic drugs. General exclusion criteria for SPECT and MRI imaging, including administration of Tc-99mDPD and gadolinium based contrast material, were applied. Ten consecutive early RA patients (eight females, two males; mean age, 49±13 years; age range, 25–68 years) were enrolled.

MRI

MRI of the more symptomatic hand was performed on a 3 Tesla system (Magnetom Trio, Siemens Healthcare, Erlangen, Germany) using a

four-channel flex coil (366×174 mm). The following imaging protocol was applied: 1) coronal fat-suppressed short tau inversion recovery (STIR) sequence (repetition time [TR], 5560 ms; echo time [TE], 31 ms; inversion time [TI], 150 ms; slice thickness, 3 mm; field of view [FoV], 120×120 mm; matrix size, 256×182 pixels), 2) coronal T1-weighted turbo spin-echo (TSE) sequence (TR, 860 ms; TE, 25 ms; FoV, 120×120 mm), 3) dynamic contrast enhanced T1-weighted sequence (TR, 333 ms; TE, 1.46 ms; FoV, 120×120 mm), 4) contrast enhanced coronal T1-weighted TSE sequence (TR, 860 ms; TE, 25 ms; FoV, 120×120 mm), axial contrast enhanced T1-weighted fat suppressed spin-echo sequence (TR, 765 ms; TE, 12 ms; FoV, 60×20 mm).

MPH-SPECT imaging

MPH-SPECT imaging was performed two hours after injection of a bodyweight adapted dose of approximately 550 MBq of Tc-99mDPD. A Picker PRISM 2000 S camera (Philips Medical Systems, Hamburg, Germany) with a MPH pyramidal collimator was used, reaching a spatial resolution <1 mm, as described elsewhere (13). The FoV was 110×100 mm, covering the metacarpophalangeal (MCP), proximal interphalangeal, and distal interphalangeal joints of the imaged hand. The rotation radius was 90 mm, and each aperture had a sensitivity of 150 cps/ MBq across the FoV. Duration of the scan was 25 min.

Imaging data analysis

Analysis focused on the MCP joints as the most affected primary joint site in early RA. Because the thumb is frequently affected by degenerative changes, MCP I was excluded. Images were reviewed by two independent, blinded readers (A.S., C.B.); discordant judgments were reviewed for consensus. Synovitis, bone marrow edema (BME), and erosions of the MCP joints II-V were scored following the accordant subscores of the Rheumatoid Arthritis MRI Score (RAMRIS). In MPH-SPECT data, region of interest (ROI) analysis with three-dimensional ROIs fitted to cover the head of the metacarpal and basis of the phalangeal bones was performed using AMIDE® software (http://amide.sourceforge.net). One clinically not involved joint (absence

of swelling and tenderness) was selected in each patient as the reference joint. Uptake ratios of all joint sites were calculated in relation to the Tc-99mDPD uptake of the reference joint to provide comparability for the group analysis.

Statistical analysis

Analysis was performed using a computer software (Statistical Package for Social Sciences version 19.0, SPSS Inc., Chicago, Illinois, USA). Intraclass correlation coefficients were used to test for interobserver reliability. Spearman correlations (referred to as R) and the phi-coefficient (referred to as R_{*}) were calculated for description of associations between image findings. Univariate analysis of variance (ANOVA) and post-hoc analysis (Tukey) were performed to test for differences among the categories of RAMRIS synovitis subscore regarding mean MPH-SPECT uptake ratio. A P value less than 0.05 was considered to indicate a significant difference. Study data are presented as mean±standard deviation.

Results

MRI

Interreader reliability for the assessment of synovitis, BME, and erosions on MRI was 0.620, 0.743, and 0.816, respectively (P < 0.01). Fig. 1 summarizes the imaging results. MRI scoring revealed synovitis in 58 MCP joints (72.5%). Synovitis was mild, moderate, and severe in 22, 26, and 10 of these joint sites, respectively; examples for mild, moderate, and severe synovitis are shown in Fig. 2. BME was found in a total of four joints, scored as mild in three joints and severe in one joint. Small bony erosions (score ≤ 2) were found in two MCP joints.

MPH-SPECT

Interreader reliability for MPH-SPECT was 0.79 (P < 0.01). Thirty-eight joint sites (47.5%) were visually determined to have increased bone metabolism (Fig. 1). The proportion of joints with elevated bone metabolism in the subgroups 1–3 of the synovitis subset of the RAMRIS was 63.6% (14/22), 46.2% (12/26), and 100% (10/10), respectively.

MPH-SPECT vs. MRI

Visually assessed increased Tc-99mD-PD uptake in MPH-SPECT correlated with synovitis (R_{ϕ} =0.574, P < 0.01) (Figs. 1, 3). Of the 38 joint sites, 32 (84.2%) had visually increased bone metabolism and showed normal MRI bone signal (Figs. 1, 4).

ROI analysis of MPH-SPECT

The mean MPH-SPECT uptake ratio for all joint sites (n=80) was 1.64±1.03 (range, 1-8.76). Mean uptake ratio in joint sites that were scored to have increased bone metabolism in visual MPH-SPECT analysis (1.94±1.38; range, 1-8.76) was significantly higher than in joint sites that were scored to have normal bone metabolism $(1.37\pm0.37; \text{ range, } 1-2.6; P = 0.012).$ Setting a measured uptake ratio of 1.74 as a threshold, increased metabolism was found in 22 joint sites (27.5%). The correlation between uptake ratio and the synovitis subscore of the RAM-RIS was weak (R=0.288; P = 0.01). The mean MPH-SPECT uptake ratio was significantly elevated in joints with severe synovitis only (Figs. 4, 5; Table).

Discussion

MPH-SPECT, based on a visual analysis, revealed increased bone metabolism in 47.5% (38/80) of imaged MCP joint

 Table. Comparison of MPH-SPECT uptake ratios between the categories of severity of synovitis (RAMRIS)

| Severity of synovitis (RAMRIS) | MPH-SPECT uptake ratio (mean±standard deviation) | Pa |
|-----------------------------------|---|---------|
| 0 | 1.38±0.42 | > 0.05 |
| 1 | 1.50±0.60 | > 0.05 |
| 2 | 1.49±0.40 | > 0.05 |
| 3 | 2.91±2.30 | < 0.001 |

RAMRIS, Rheumatoid Arthritis MRI Score.

^a*P* is for comparison between the corresponding group and all other groups with analysis of variance. The MPH-SPECT uptake ratio is significantly elevated in the group of joints with severe synovitis (score 3), compared to all other groups.



Figure 1. MPH-SPECT image (*background*) showing the FoV of the SPECT camera. Boxes represent the analyzed metacarpophalangeal joint sites in all ten patients containing the data of the visual MPH-SPECT (+, increased Tc-99mDPD uptake) and MRI (Syn, RAMRIS synovitis subscore; Ede, RAMRIS edema subscore; Ero, RAMRIS erosion subscore) analysis.

sites. Using semiquantitative assessment (ROI analysis) of MPH-SPECT images, 27.5% (22/80) of the imaged joint sites had increased bone metabolism, while bone erosions and even BME, as the earliest sign of inflammatory bone involvement (5), was depicted by MRI in only 7.5% (6/80). This data corroborate the previously described mismatch (13) in sensitivity between MPH-SPECT and MRI for the detection of early bone inflammation in RA.

Since Tc-99mDPD uptake mainly reflects increased osteoblast activity (8), MPH-SPECT may complement our knowledge on the pathophysiology of inflammatory joint changes. Histopathological studies of joints in RA patients show accumulation of osteoblasts adjacent to focal bone erosions (16) and joint sites exposed to inflammatory synovial tissue (17) representing an attempt of reactive bone repair. Increased tracer uptake in MPH-SPECT can thus be interpreted as visualization of this pathomechanism. Our data therefore suggest that reactive osteoblastic repair can be visualized in early RA as a counterpart to periarticular bone loss, a common event of RA (18). We found that bone metabolism in joints with absence of synovitis, or mild and moderate synovitis was not significantly altered, while a significant increase was detected in joints with severe synovitis. This finding indicates that there might be a threshold for bone infiltration by inflammatory



Figure 2. a-c. Axial contrast enhanced T1 fat suppressed images showing examples for mild (a), moderate (b), and severe (c) synovitis of the metacarpophalangeal joints in an early RA patient.



Figure 3. a-c. Axial contrast enhanced T1 fat suppressed image (a), MPH-SPECT image (b), and MPH-SPECT/MRI fusion image (c) of the left hand of an early RA patient showing increased bone metabolism and adjacent synovitis in the metacarpophalangeal joint IV.



Figure 4. a–c. Coronal STIR (a) and MPH-SPECT image (b) of the left hand metacarpophalangeal joints of an early RA showing normal bone marrow signal on MRI but increased bone metabolism in MPH-SPECT. The MPH-SPCT/MRI fusion image (c) demonstrates the mismatch of those findings in the proximal portion of the metacarpophalangeal joint II.



Figure 5. Uptake ratio in MPH-SPECT and severity of synovitis (RAMRIS) in metacarpophalangeal joints (outliers are marked with *circles* and *asterisks*, and included in the analysis).

synovial tissue and that osteitis might be preferentially driven outside-in by synovitis. In support of this hypothesis, Jiminez-Boj et al. (17) reported histopathological evidence for direct penetration of inflammatory synovial tissue through the cortical bone barrier and induction of inflammatory changes in the adjacent bone marrow. Though not reaching statistical significance, we detected a higher bone metabolism in joints, which showed BME on MRI, indicating that increased bone metabolism is found in joints with osteitis. Whether increased Tc-99mDPD uptake constitutes a precursor of BME or erosion must be evaluated in future longitudinal studies. MPH-SPECT might be a valuable tool for the early detection of patients that are at high risk for an erosive disease course and thus could contribute to individualized therapeutic approaches. This pilot study was generated to explore potential justification for larger population studies. Our preliminary results require a more detailed analysis, including mini-athroscopic biopsy and histopathology, and validation of the threshold for the semiquantitative MPH-SPECT analysis in normal volunteers.

In conclusion, in early RA, molecular imaging with MPH-SPECT detects higher rates of inflammatory bone involvement compared to MRI. Our preliminary data suggest that osteitis is related to severe synovitis.

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Conflict of interest disclosure

The authors declared no conflicts of interest.

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