Bone Edema Determined by Magnetic Resonance Imaging Reflects Severe Disease Status in Patients with Early-Stage Rheumatoid Arthritis

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ABSTRACT. ***Objective***. To determine the significance of bone edema, detected by magnetic resonance imaging (MRI), in early-stage rheumatoid arthritis (RA).

Methods. We simultaneously examined serologic variables, MRI of wrist sites and finger joints of both hands, clinical disease activity score (DAS), and HLA-DR typing at entry in 80 patients with early-stage RA.

Results. The number of bones scored as positive for bone edema correlated with the number of sites scored as positive for MRI synovitis and MRI bone erosion, rate of enhancement (E-rate), and serum C-reactive protein (CRP), matrix metalloproteinase 3 (MMP-3), and interleukin 6 (IL-6). Findings for MRI synovitis and MRI bone erosion, E-rate, CRP, MMP-3, IL-6, seropositivity, and titer of anti-cyclic citrullinated peptide antibody (anti-CCP antibody), DAS28-CRP and HLA-DRB1*0405 allele carriership, were significantly higher in the positive versus the negative bone edema group.

Conclusion. Bone edema based on our scoring system may reflect severe disease status in patients with early-stage RA. However, its clinical value at entry in prognostication of RA should be examined through prospective clinical followup studies. (First Release Oct 1 2007; J Rheumatol 2007;34:2154–7)

Key Indexing Terms:
EARLY-STAGE RHEUMATOID ARTHRITIS MAGNETIC RESONANCE IMAGING
BONE EDEMA SEROLOGIC VARIABLES HLA-DRB1*0405 ALLELE

Evaluation of magnetic resonance imaging (MRI) in rheumatoid arthritis (RA) has been analyzed using the OMERACT 5 RA-MRI scoring system (RAMRIS)[1,2] and by others[3,4]; however, the scoring process is complicated. We evaluated MRI features by imaging only wrist sites and finger joints in early-stage RA using different qualification parameters[5,6].

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MATERIALS AND METHODS

Enrolled patients were from the Early Arthritis Clinic, First Department of Internal Medicine, Graduate School of Biomedical Sciences, Nagasaki University. The study consists of 80 patients with early-stage RA, who gave their informed consent to the protocol that was approved by the Institutional Review Board of Nagasaki University. Median disease duration from onset of symptoms to entry was 3 months. Disease duration in all 80 patients was < 2 years, similar to a recent report[7]. Diagnosis was made based on 1987 American College of Rheumatology (ACR) criteria for RA[8]. Thirty-six patients were already classifed as RA at entry, while the remaining 44, who were classified as undifferentiated arthritis at entry, developed to RA later. Median modified Genant-Sharp score at entry by plain radiography was 0.26.

The following variables were examined at entry. Serologic tests included matrix metalloproteinase-3 (MMP-3), anti-cyclic citrullinated peptide (anti-CCP), and interleukin 6 (IL-6). Clinical disease activity was qualified by DAS28 (Disease Activity Score 28-C-reactive protein (DAS28-CRP). High resolution analysis of HLA-DRB1 genotyping was performed, as described[7,9], by polymerase chain reaction. MR images of both wrists and finger joints (1.5 T system, Sigma, GE Medical Systems, Milwaukee, WI, USA) were evaluated for bone edema, bone erosion, and synovitis in 15 sites in each finger and wrist, i.e., distal radioulnar joint, radiocarpal joint, mid-carpal joint, first carpometacarpal joint, 2nd-5th carpometacarpal joint (together), 1st-5th metacarpophalangeal joints (proximal interphalangeal) separately (total 30 sites in both hands) as reported[5,6]. MR images were interpreted independently by 2 board-certified radiologists experienced in musculoskeletal imaging (MU and ST) who were blinded to patients' clinical status. Both radiologists read each image according to the definition as described[3-6], and disagreements were resolved by consensus. Degree of MRI features was evaluated per our recent report: synovitis; number of sites scored positive for MRI

synovitis and E-rate, bone edema; number of bones scored positive for bone edema, bone erosion; number of bones scored positive for MRI bone erosion, respectively[5].

Differences between groups were examined using the Mann-Whitney U test and chi-square test. A correlation between the 2 variables was calculated by Spearman's rank correlation. A p value < 0.05 denoted a statistically significant difference.

RESULTS

Representative MR images are shown in Figure 1. The number of bones scored as positive for bone edema clearly correlated with the number of sites scored as positive for MRI synovitis and MRI bone erosion, mean E-rate from 30 sites, bone erosion number, CRP, MMP-3, and IL-6 as shown in Figure 2.

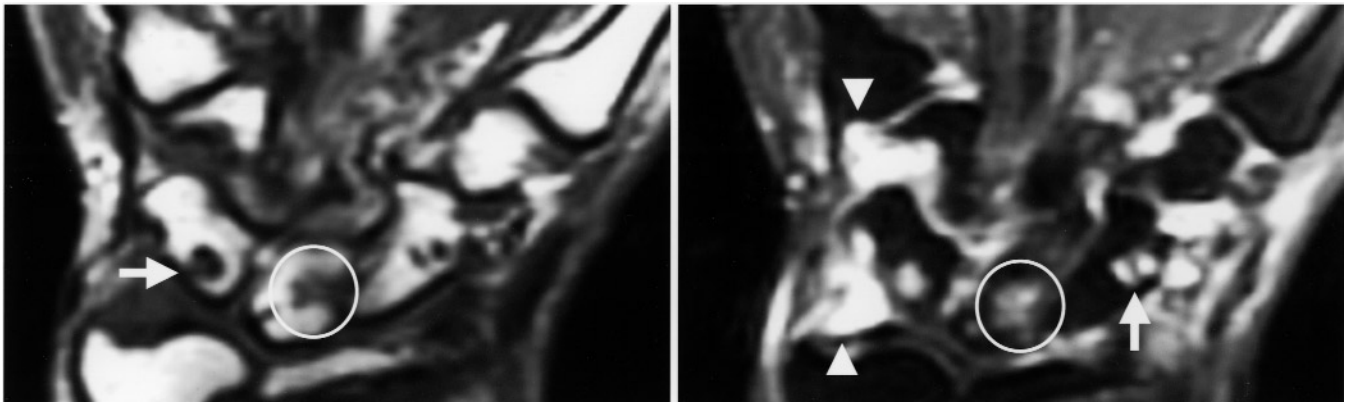

Figure 1. Representative MR images of patients with early-stage RA. T1-weighted spin-echo images show bone edema (circle), bone erosion (arrow), and synovitis (arrowheads). Right panel: gadolinium-diethylenetriamine-enhanced image.

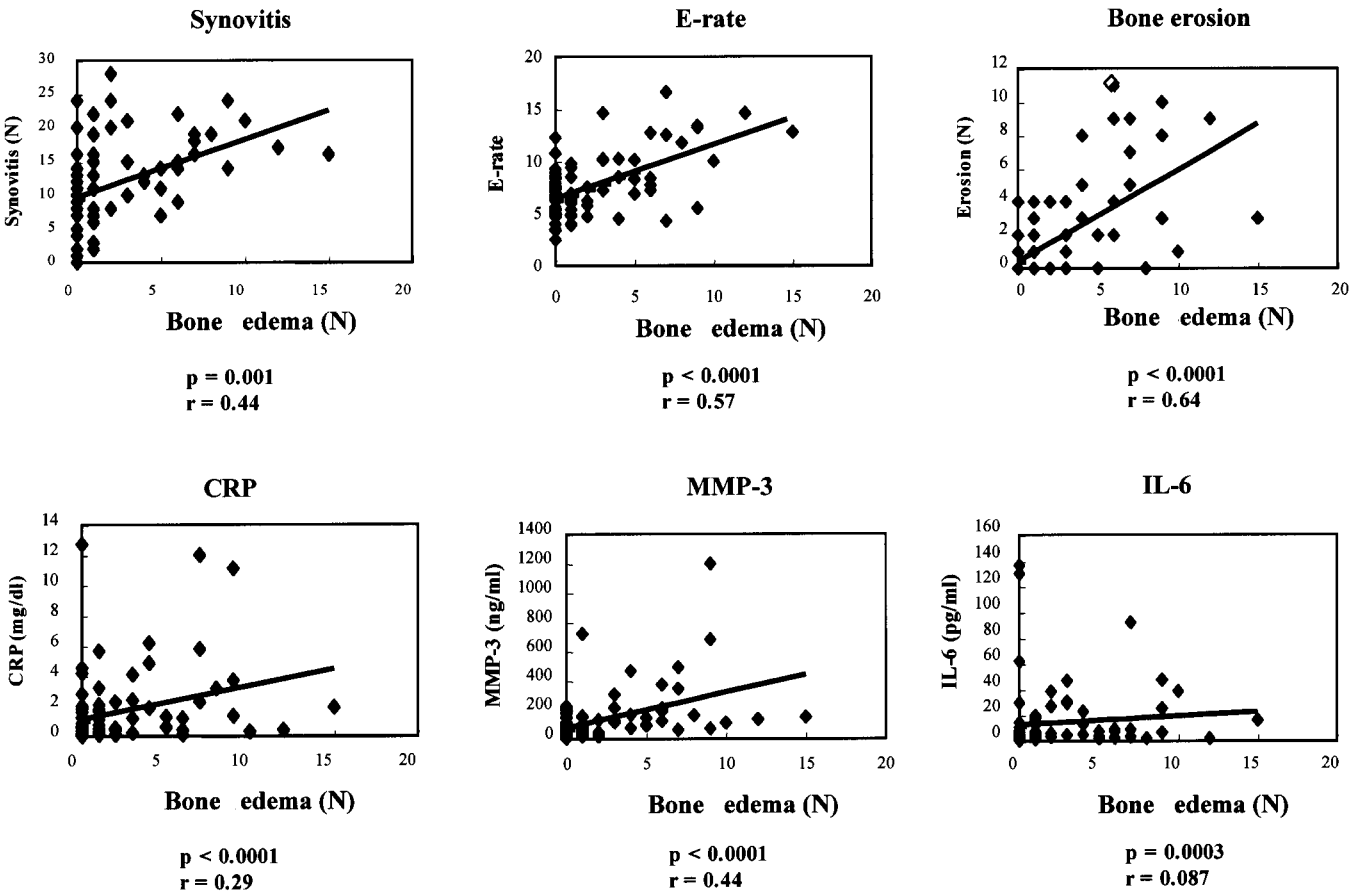

Figure 2. Positive correlation between the number of bones scored as positive for bone edema and the number of sites scored for MRI synovitis and MRI bone erosion, enhancement rate (E-rate), serum concentrations of CRP, MMP-3, and IL-6.

Patients with early-stage RA were divided into 2 groups: with or without bone edema. MRI evidence of synovial inflammation and bone erosion was more remarkable in bone edema-positive patients. Seropositivity and titer for anti-CCP antibody, CRP, MMP-3, IL-6, and DAS28-CRP were also higher in the bone edema-positive group (Table 1). Positive correlation between DAS28-CRP and the number of bones scored as positive for bone edema was also identified by Spearman's rank correlation test (p = 0.00026, rs = 0.398).

In 36 of the 80 (45%) patients with early-stage RA, we confirmed at least one HLA-DRB1*0405 allele, the most frequent shared epitope in Japanese RA patients[9]. This allele was more predominantly distributed in the bone edema-positive group versus the -negative group (Table 1). Our data also showed that significantly more patients who were positive for anti-CCP antibody and HLA-DRB1*0405 allele (N = 26) had a positive score for bone edema (77%) compared to patients who were negative for both these markers (N = 16), in whom bone edema was scored in only 25% (p = 0.0013).

DISCUSSION

Trying to solve the complexity of standard MRI scoring methods, we semiquantitatively evaluated MRI features. The present data suggest that our score, especially bone edema score, classified the disease status of early-stage RA.

Employing prospective analysis, van Gaalen, *et al* recently showed that patients with early-stage RA at entry who are positive for both anti-CCP antibody and HLA-DRB1 shared epitope developed severe erosive disease[7]. Considering bone edema is a forerunner of bone erosion[10], our findings that bone edema-positive early-stage RA patients are preferentially distributed in the subgroup positive for anti-CCP antibody and HLA-DRB1*0405 allele support the findings of van Gaalen, *et al* as well as the prognostic value of bone edema.

Our results suggest that bone edema in patients with early-stage RA develops through an inflammatory synovial microenviroment with specific HLA-antigen interaction, and our evaluation method for MRI may be an alternative for the standard methods. However, since a therapeutic regimen was already administered in some patients at entry to the study, its clinical value should be verified through prospective followup studies.

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Table 1. Clinical features in early-stage RA with or without bone edema. All the variables were highly significant in the bone edema-positive group.

Variable	Bone Edema, n = 45	No Bone Edema, n = 35	p
CRP, mg/ml*	2.08 ± 2.62	1.03 ± 2.33	< 0.0001
MMP-3, ng/ml*	178.2 ± 225.4	71.4 ± 61.9	0.002
No. of sites scored as positive for MRI synovitis*	13.9 ± 5.9	8.6 ± 5.8	0.0002
Mean E-rate from 30 sites*	8.34 ± 3.26	6.56 ± 2.10	0.03
Bone erosion			
%†	60.0	25.7	0.02
n*	2.71 ± 3.31	0.37 ± 0.81	0.02
IL-6, pg/ml	14.7 ± 17.2	13.1 ± 32.1	0.0003
Anti-CCP antibody			
%	77.8	52.3	0.02
U/ml*	218.2 ± 399.2	82.4 ± 182.2	0.01
DAS28-CRP	4.54 ± 1.02	3.88 ± 1.18	0.008
HLA-DRB1*0405, %	57.8	28.6	0.009

* Mann-Whitney U test. † Chi-square test, as described in text.

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