Correlation of matrix metalloproteinase-9 level, erythrocyte sedimentation rate, rheumatoid factor, and the duration of illness with radiological findings in rheumatoid arthritis patients

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ABSTRACT

Background: Rheumatoid arthritis (RA) is a common autoimmune disease of the joint indicated by chronic inflammation of synovium, cartilage destruction, and osteopenia. The end results of RA are joint deformity and disability that will decrease the quality of life of the patients. Until now there is not a specific marker to assess the process of joint and bone damage in RA. Available markers such as C-reactive protein and erythrocyte sedimentation rate (ESR) indicate more about the inflammatory status of the patient. The discovery of matrix metalloproteinases (MMPs) enzyme overexpression in RA has brought a new hope for the discovery of more specific markers of joint damage.

Objective: To study the correlation of MMP-9 level, ESR, rheumatoid factor (RF), and the duration of illness with joint damage in RA patients.

Methods: A cross-sectional study was conducted on RA outpatients in rheumatology clinic at Cipto Mangunkusumo General Hospital, Jakarta from January to October 2009. From the patients who fulfilled the inclusion criteria and did not fulfill the exclusion criteria, blood sample was collected for MMP-9 level, RF, and ESR examinations; hand radiography (posterior-anterior view) was also taken.

Results: From the study of 46 patients, we found a significant correlation between MMP-9 level and radiographic feature of bone erosion ($r = 0.3$, $p = 0.02$) and between the duration of illness and Sharp score ($r = 0.36$, $p = 0.014$). There was no correlation between ESR and radiological findings nor between RF and radiological findings. Linear regression analysis showed the duration of illness as the most influencing factor to radiological findings in RA patients.

Conclusion: We found a significant correlation between MMP-9 level and radiographic feature of bone erosion, and between the duration of illness and radiological findings in RA patients.

Matrix metalloproteinases (MMPs) are a group of enzymes first known to be involved in morphologic changes of tadpole. This group of enzymes, later known to be able to degrade the substrate of extracellular matrix, is categorized based on the degraded specific substrate. Until now there have been more than 20 MMPs enzymes found. It is assumed that MMPs can interfere with cell behavior including cell apoptosis, migration, and proliferation.[1]

Matrix metalloproteinase-9 has telopeptidase activity toward collagen and agrecanase, the minor components of joint cartilage, thus MMP-9 is presumed to play a role in bone resorption. Rheumatoid arthritis (RA) itself is an autoimmune disease mainly affecting the joints besides other organs. The disease is indicated with symmetrical synovitis and bone erosion with the final result of joint deformity. There is a rather complex cytokine network in RA, but the dominant proinflammatory cytokines are tumor necrosis factor α (TNFα) and interleukin-1.[2]

Posthumus et al and Young Min et al reported that the high level of MMP-3 was correlated with the progression of radiographic joint damage, hence the high level of MMP-3 at the initial time of diagnosis is the reason to give anti-TNFα.[3,4] However, Tsukuhara reported that genetic polymorphism promoting MMP-3 in AR patient in Japan did not influence the joint damage. It was different from the RA population in Europe.[5] Gruber et al stated that there was increase of MMP-9 level in RA patients. Chang et al also reported the increase of MMP-9 level in RA patients in Taiwan. Matrix metalloproteinase-9 was thought to play a role in joint damage in RA.[6,7]

It is assumed that MMP-9 plays more roles than other MMPs in joint damage in RA. Meanwhile, other "traditional" inflammatory markers such as rheumatoid factor (RF) and erythrocyte sedimentation rate (ESR) are still being used often to predict radiological damage. Based on those ideas, we wanted to study the correlation of MMP-9 level, ESR, RF, and the duration of illness with radiographic joint damage in RA patients.

METHODS
Study design
This was a cross-sectional study conducted at rheumatology clinic at Cipto Mangunkusumo

General Hospital (CMGH), Jakarta involving 46 RA patients from January to October 2009. The sample size was calculated using formula for correlation coefficient for single sample. Dependent variable in this study was radiological Sharp score, while the independent variables were MMP-9 level, ESR, RF level, and the duration of illness.

Subjects

Inclusion criteria were RA patients fulfilling the 1987 American College of Rheumatology criteria and agreed to be included in the study. Patients with chronic kidney disease, malignancy, chronic obstructive pulmonary disease, and systemic infection were excluded from the study. The study protocol had been approved by the appropriate local ethical board. All patients were then asked to give informed consent.

Measurement

Blood was collected for MMP-9 level, RF level, and ESR examinations. Matrix metalloproteinase-9 was examined in duplicate using enzyme-linked immunosorbent assay method from Bender MedSystem GmbH performed at Integrated Laboratory (*Makmal Terpadu*) at University of Indonesia School of Medicine, Jakarta. The result was in ng/mL. ESR was stated in mm/hour and RF was in IU/mL. Hand radiography with posterior-anterior view was also performed on the subjects with computed tomography at Department of Radiology at CMGH using Kodak CR975 System. The images were then interpreted by consultant radiologist and reported as Sharp score. Sharp score is a cumulative of two scores: joint space narrowing score in 16 hand joint area (0 = no joint space narrowing to 4 = no joint space) and bone erosion score in 17 hand joint area (0 = no bone erosion to 5 = extending erosion).

Statisitical methods

The collected data were analyzed using Statistical Package for the Social Sciences (SPSS) program. We used multivariate analysis for statistical test of subject characteristics and bivariate analysis for correlation test using Pearson's correlation test (or Spearman's test for abnormally distributed data), then continued with multivariate analysis.

RESULTS

Of the 46 subjects we found the characteristics as follows: 40 subjects (87.0%) were female and 6 subjects (13.0%) were male. Mean age was 48.61 years and mean duration of illness was 4.83 years. Mean tender joint count was 5.42 and mean swollen joint count was 2.54. Mean total Sharp score, erosion score, and joint space narrowing score were 8.76, 3.50, and 5.37, respectively (table 1).

Table 1   Characteristics of subjects

Characteristics	Median (range)
Age, years	50.0 (29–67)
Tender joint count	3.0 (0–22)
Swollen joint count	0.0 (0–14)
ESR, mm/hr	52.20 (3–116)
RF level, IU/mL	22.77 (5.4–300)
MMP-9 level, ng/mL	112.17 (38.73–154.47)
Duration of illness, years	3.56 (1–14)
Joint space narrowing score	3.0 (0–21)
Bone erosion score	2.0 (0–18)
Total Sharp score	5.0 (0–34)

ESR, erythrocyte sedimentation rate; RF, rheumatoid factor; MMP-9, matrix metalloproteinase-9.

There was not any correlation of MMP-9 level, ESR, or RF with the total Sharp score, but there was a significant correlation between the duration of illness and the total Sharp score (table 2). We also found a significant correlation between MMP-9 level and bone erosion score ($r = 0.3$, $p = 0.02$).

Table 2   Correlation of matrix metalloproteinase-9 (MMP-9) level, rheumatoid factor (RF) level, erythrocyte sedimentation rate (ESR), and the duration of illness with the Sharp score

	Sharp score r (p Value)
MMP-9 level	0.181 (0.115)
RF level	0.194 (0.098)
ESR	0.104 (0.246)
Duration of illness	0.361 (0.014)

MMP-9, matrix metalloproteinase-9; RF, rheumatoid factor; ESR, erythrocyte sedimentation rate.

From the analysis of receiver operating characteristic curve, we obtained the cut-off point of 95.02 ng/mL for MMP-9 level with 72.72% sensitivity and 40.00% specificity. On the other hand, the cut-off point for the duration of illness was 39.0 months with 75.0% sensitivity and 63.33% specificity. In multivariate linear regression analysis we found the duration of illness as the most influencing factor to radiographic joint damage ($r = 0.299$, $p = 0.043$).

DISCUSSION

In this study we found that ESR and RF did not correlate with joint damage in RA patients. This result is different from previous studies done overseas. Caruso et al[8] and Combe et al[9] reported that ESR was the prognostic factor for radiographic joint damage, while Vitttecoq et al[10] reported that RF was the predictor for radiographic progression in RA patients. The difference in results could be caused in part by the study design used: those studies were prospective study, while ours was a cross-sectional study. We found a significant correlation between MMP-9 level and bone erosion score ($r = 0.3$, $p = 0.02$). It fitted the theory that MMP-9 has telopeptidase activity toward collagen, thus it is assumed to play a role in bone

resorption. Engsig et al stated that MMP-9 plays important role in osteoclasts recruitment and migration to diaphysis in long bone formation, in conformity with theory stating that MMPs also play a role in cell behavior.[11] Recruited osteoclasts in RA will become hyperactive through the receptor activator for nuclear factor-κB (RANK) protein in osteoclasts membrane, thus the osteoclasts would become active and resorp the bone. In this study, the duration of illness was significantly correlated with radiological findings (r = 0.36, p = 0.014). It fitted the study of Caruso et al which stated that the duration of illness was the most important factor that correlates with radiographic joint damage.[8]

CONCLUSIONS

We found a significant correlation between MMP-9 level and radiographic bone erosion, and between the duration of illness and radiological findings in RA patients. Further studies are needed to investigate the role of MMPs in RA.

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