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Published in:
Rheumatology

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
1999

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

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Serum levels of matrix metalloproteinase-3 in relation to the development of radiological damage in patients with early rheumatoid arthritis

M. D. Posthumus, P. C. Limburg, J. Westra, H. A. Cats, R. E. Stewart, M. A. van Leeuwen and M. H. van Rijswijk

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Abstract

Objective. To evaluate the significance of serum matrix metalloproteinase-3 (MMP-3) levels in relation to the development of radiological damage (X-ray damage) in early rheumatoid arthritis (RA).

Methods. Serum MMP-3 levels were measured in 46 healthy controls (CTRL), 19 osteoarthritis (OA) and 78 RA patients with joint symptoms for < 1 yr at presentation (T0): 48 patients without and 30 with X-ray damage at T0. Serum MMP-3, measured by ELISA, and X-ray damage, scored according to Sharp’s method, were assessed at 0, 6, 12 and 24 months.

Results. MMP-3 levels in CTRL and OA were low or undetectable with no differences between the groups (P = 0.19). Levels in RA were higher than in CTRL (P < 0.01). Initial MMP-3 levels in patients with X-ray damage at T0 (n = 30) were higher than the levels in patients without any X-ray damage during follow-up (n = 19) (P < 0.01), but were not different from those in patients who developed X-ray damage during the study (n = 29) (P = 0.11). In the patients without X-ray damage at T0, there was a significant correlation between MMP-3 at T0 and the total X-ray damage after 6 months (r = 0.34, P = 0.02) and 12 months (r = 0.32, P = 0.03). This correlation was almost exclusively determined by joint space narrowing in the Sharp score.

Conclusion. The serum MMP-3 level seems to be an indicator for the development of radiological damage in patients with early RA and appears to be particularly indicative of cartilage degradation.

Key words: Serum matrix metalloproteinase-3, Early rheumatoid arthritis, Radiological damage.

Matrix metalloproteinases (MMPs) are proteolytic enzymes that can degrade extracellular matrix components [1]. These enzymes are synthesized as latent pro-enzymes, contain a zinc binding active site, and require Ca2+ and proteolytic cleavage for activation. The MMP family includes four different groups of enzymes: (I) collagenases (interstitial collagenase 1 or MMP-1, neutrophil-type collagenase 2 or MMP-8 and collagenase 3 or MMP-13); (II) gelatinases (gelatinase A or MMP-2 and gelatinase B or MMP-9); (III) stromelysins (stromelysin-1 or MMP-3, stromelysin-2 or MMP-10); (IV) others (matrilysin, stromelysin-3, metalloelastase and membrane-type MMPs which are not secreted but anchored into the membrane). The activity of the MMPs can be regulated either by modulation of pro-enzyme production and/or activation, or by changes in the levels of inhibitors of MMPs such as a2-macroglobulin and tissue inhibitors of matrix metalloproteinases (TIMPs) [2, 3]. An imbalance between these inhibitors and the proteases conceivably leads to matrix degradation [4, 5].

The MMPs play an important role both in normal physiological processes and in pathological conditions such as arthritis. In patients with rheumatoid arthritis (RA), the MMPs play a major role in the destruction of cartilage and other components of connective tissue in the joints. MMPs are released by synovial fibroblasts, chondrocytes, macrophages, neutrophils and endothelial cells in response to pro-inflammatory cytokines like interleukin-1 (IL-1), tumour necrosis factor alpha (TNF-α), and growth factors such as epidermal growth factor and platelet-derived growth factor [6, 7].

Submitted 16 February 1999; revised version accepted 30 April 1999.

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Of the MMP family, MMP-3 is thought to play a prominent role in the pathogenesis of RA even though it is not the only key enzyme in matrix degradation in this disease [8]. MMP-3 is capable of degrading many components of matrix proteins in the synovial joint, including proteoglycans, gelatins, laminin, fibronectin and collagens III, IV, IX, X [1, 9–11]. The enzyme has been localized in the fibroblast-like synovial lining cell of rheumatoid synovium [12, 13] and in RA cartilages [4, 5]. It is secreted as a latent pro-enzyme resulting in highly elevated MMP-3 levels in synovial fluid of RA patients [14–16]. Although serum levels are (300–500 times) lower, there is a highly significant correlation with matched synovial fluid levels, indicating that serum MMP-3 is derived mainly from the inflamed synovium [14, 16–20]. Levels of activated MMP-3 are also highly increased in synovial fluid [21], but measurement of activated MMP-3 in serum will be very difficult, if not impossible, because of the high serum levels of α2-macroglobulin, which encloses the activated proteinase completely [3].

In RA serum, MMP-3 could be a specific marker of joint inflammation and destruction because it is almost exclusively produced locally, in the inflamed synovium. In that case, it could be used in the early identification of patients with aggressive destructive disease, which is important for therapeutic reasons [22].

Several other features, such as age, HLA-DR4, rheumatoid factor (RF) and C-reactive protein (CRP) production, also appear to be prognostic for the final outcome [23]. Although CRP is a good parameter for prognostic purposes [24] and for monitoring treatment effects, it is an indicator of inflammation in general, which may be influenced by other stimuli of the acute-phase response; this in contrast with MMP-3 [17].

Previous studies of serum MMP-3 levels in RA concerned patients with a long disease duration [14, 16, 18, 20]. Investigation in an early phase of the disease and, in particular, in a group of patients without initial radiological damage (X-ray damage) has, to our knowledge, not been reported.

In the present study, we measured the levels of MMP-3 in sera from patients with early RA without X-ray damage at presentation and compared these with serum levels in RA patients with X-ray damage already at presentation, osteoarthritis (OA) patients and healthy controls (CTRL). In the group of RA patients without initial X-ray damage, we analysed whether serum MMP-3 levels have a predictive value for the development of X-ray damage. Furthermore, we investigated in this selected group of RA patients the relationship between serum MMP-3 levels and CRP.

Patients and methods

Patients

Seventy-eight patients with RA, 19 patients with OA and 46 CTRL were studied. The RA patients were selected from a cohort of patients with RA, according to the 1987 ACR criteria [25], with joint symptoms existing for <1 yr at presentation and who had not previously received disease-modifying anti-rheumatic drugs (DMARDs). These patients participated in a prospective follow-up study at the department of rheumatology at the Groningen University Hospital. During follow-up, patients were treated with non-steroidal anti-inflammatory drugs and DMARDs as indicated clinically. Guidelines for the sequence of the different second-line drugs were as follows: hydroxychloroquine or sulphasalazine as first-choice therapy, followed in order by i.m. gold, D-penicillamine, azathioprine or methotrexate. Low-dose corticosteroids could be administered as adjuvant therapy.

Out of this cohort, 48 consecutive RA patients without X-ray damage and a randomly chosen group of 30 RA patients with X-ray damage due to RA at presentation were selected. In the group of 48 RA patients without initial X-ray damage, 19 patients did not develop X-ray damage during the 2 yr of follow-up [RA-00 group; initially no X-ray damage (= 0) and after 2 yr no X-ray damage (= 0)]. The remaining 29 patients developed X-ray damage (1 or more Sharp points) during the 2 yr of follow-up [RA-0X group; initially no X-ray damage (= 0), after 2 yr X-ray damage (= X)].

Clinical (number of painful joints, number of swollen joints, Ritchie articular index) and laboratory (CRP) investigations were performed at monthly visits during 2 yr.

Radiographs of hands and feet were obtained at study entry and every 6 months during 2 yr. Joint damage in the hands and feet was assessed by Sharp’s method with some modifications, in particular inclusion of foot joints, as described by Van der Heijde [26] and Van der Heijde et al. [27]. By this method, joint space narrowing and erosions are scored separately and combined in a total X-ray damage score. The radiographs were scored without knowledge of clinical and laboratory data in chronological order per patient by two observers (MvL and HAC). The interobserver agreement was 0.90 and the intra-observer agreements were 0.96 and 0.99 for the two observers, respectively. The radiographic score in the group of RA patients with initial X-ray damage (RA-XX) was 5 or more at study entry. For analysis, we used the variables at presentation (T0) and after 6, 12 and 24 months. Of the group of 30 RA patients with X-ray damage at presentation (RA-XX), only the variables at study entry were used. OA was diagnosed from clinical and radiological investigations using the ACR criteria for OA [28–30]. The CTRL were blood bank donors.

Measurement of MMP-3

Serum samples were obtained at 0, 6, 12 and 24 months. MMP-3 levels were determined with an MMP-3 ELISA developed in our laboratory. In short, 96-well plates were pre-coated with the F(ab)2 fragment of goat anti-mouse Ig, 1 µg/ml (Jackson ImmunoResearch Labs, West Grove, PA, USA). Next, a mouse monoclonal antibody against human MMP-3, clone 55-2-A4 (clone
Statistical analysis

ELISA. In 192 serum samples, there was a good correlation between groups were analysed by

Other laboratory measurements

B) [31] (Oncogene, Cambridge, MA, USA) was coated, 0.2 μg/ml. Serum samples were analysed in 2-fold serial dilutions in High Performance ELISA buffer (CLB, Amsterdam, The Netherlands) and incubated during 1 h. After washing, bound MMP-3 was detected with a biotinylated polyclonal sheep anti-MMP-3 (The Binding Site, Birmingham, UK) in combination with streptavidin-E⁺ (CLB, Amsterdam, The Netherlands). Peroxidase activity was determined using tetramethylbenzidine as substrate. MMP-3 levels were calculated in the linear range of the assay from a standard curve (10–1500 ng/ml) using an RA synovial fluid, which was standardized against the BIOTRAK® standard (see below). The intra-assay coefficient of variation (CV) was 8.9%, the inter-assay CV was 10.1%. With an immunoblot, we have demonstrated that both the monoclonal and the polyclonal antibody reacted with active MMP-3 as well as with pro-MMP-3 (data not shown). Treatment of the sera with p-aminophenyl mercury acetate (APMA) [32, 33] to activate pro-MMP-3 did not influence results in the ELISA. Furthermore, it was demonstrated that RFs do not react in this assay and do not interfere with measurement of MMP-3.

In the group of 48 patients without initial radiological damage (RA-00/0X), serum MMP-3 levels were also measured in the BIOTRAK® MMP-3 ELISA kit (Amersham, ‘s Hertogenbosch, The Netherlands) according to the manufacturer’s recommendations at 0, 6, 12 and 24 months.

Measurement of MMP-3

In the group of 48 patients without initial radiological damage (RA-00/0X), the serum MMP-3 levels were determined with the MMP-3 ELISA developed in our own laboratory and with the BIOTRAK® MMP-3 ELISA. In 192 serum samples, there was a good correlation between the two tests (r = 0.96, P < 0.01). Further serum MMP-3 measurements and calculations were performed with our own MMP-3 ELISA.

Results

Characteristics of control subjects, OA and RA patients are summarized in Table 1.

All OA patients had OA of the hands according to the ACR criteria. Nine out of 19 patients had also OA of the knees or hips. There was one male OA patient with a high CRP of 170 mg/l due to an epididymitis and one female OA patient with a CRP level of 44 mg/l who was diagnosed as having polymyalgia rheumatica as well. The CRP levels of the other 17 OA patients were low (median 3 mg/l, range 2–21 mg/l).

In the group of 48 RA 00/0X patients, 44 (92%) were treated with DMARDs and low-dose corticosteroids were given as adjuvant treatment in six patients (13%). There were no differences between the RA groups in age, gender, RF positivity, joint pain score, joint swelling score and Ritchie articular index. Disease duration was shorter in the RA-00/0X group (P < 0.01). There was a borderline significant difference in initial CRP levels between the RA-00/0X and RA-XX groups (P = 0.05).

Table 1. Characteristics of the rheumatoid arthritis (RA), osteoarthritis (OA) patients and healthy controls (CTRL) at study entry

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>RA without radiological damage at presentation (n = 48)</th>
<th>RA with radiological damage at presentation (RA-XX) (n = 30)</th>
<th>Osteoarthritis (OA) (n = 19)</th>
<th>Controls (CTRL) (n = 46)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>47.5 (16–76)</td>
<td>45.0 (18–71)</td>
<td>59.0 (52–73)</td>
<td>41.5 (23–65)</td>
</tr>
<tr>
<td>Gender, female/male (% female)</td>
<td>31/17 (65%)</td>
<td>18/12 (60%)</td>
<td>17/2 (89%)</td>
<td>32/14 (70%)</td>
</tr>
<tr>
<td>Disease duration (months)</td>
<td>4.6 (1.5–12)</td>
<td>8.0 (1.5–12)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Rheumatoid factor, +/− (%+)</td>
<td>34/14 (71%)</td>
<td>24/6 (80%)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Joint pain</td>
<td>16.0 (2–44)</td>
<td>14.5 (1–30)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Joint swelling</td>
<td>12.5 (1–36)</td>
<td>10.5 (1–28)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Ritchie</td>
<td>13.5 (2–50)</td>
<td>12.0 (1–30)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>CRP</td>
<td>11.0 (1–232)</td>
<td>32.0 (1–250)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Sharp score</td>
<td>0</td>
<td>12.0 (5–46)</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Values are the median and range. RA-00: at presentation no radiological damage (= 0), after 2 yr no radiological damage. RA-0X: at presentation no radiological damage (= 0), after 2 yr radiological damage; ≥ 1 Sharp point (= X). RA-XX: at presentation already radiological damage; ≥ 5 Sharp points (= X), after 2 yr radiological damage (= X).

Notes:

1. RA-00/0X vs RA-XX P < 0.01.
2. RA-00/0X vs RA-XX P = 0.05.

Whitney U-test. Logistic regression analysis was performed with radiological damage as dependent variable and serum MMP-3 as independent variable at different time points. P values of < 0.05 were considered significant.
Table 2. Serum levels of matrix metalloproteinase-3 (MMP-3) (ng/ml) in rheumatoid arthritis (RA), osteoarthritis (OA) patients and healthy controls (CTRL) at study entry

<table>
<thead>
<tr>
<th></th>
<th>RA without radiological damage at presentation (RA-00 and RA-0X) (n = 48)</th>
<th>RA with radiological damage at presentation (RA-XX) (n = 30)</th>
<th>Osteoarthritis (OA) (n = 19)</th>
<th>Controls (CTRL) (n = 46)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMP-3</td>
<td>33.5 (5–1460)(^b)</td>
<td>95.5 (5–1800)(^a)</td>
<td>20.0 (5–66)</td>
<td>19.6 (5–61)(^a)</td>
</tr>
</tbody>
</table>

Values are the median and range. RA-00: at presentation no radiological damage (= 0), after 2 yr no radiological damage. RA-0X: at presentation no radiological damage (= 0), after 2 yr radiological damage; ≥1 Sharp point (= X). RA-XX: at presentation already radiological damage; ≥5 Sharp points (= X), after 2 yr radiological damage.

**Initial serum MMP-3 level in CTRL, OA and RA patients**

Serum levels of MMP-3 at study entry are summarized in Fig 1 and Table 2. In CTRL, the serum MMP-3 levels were undetectable (<10.0 ng/ml) or low. In these control subjects, the serum MMP-3 levels in men were higher than those in women (P < 0.01). Sex differences were not found in the groups of OA and RA patients. No differences were found in serum MMP-3 levels between CTRL and OA patients (P = 0.19). The serum MMP-3 levels in RA patients were higher in comparison with the CTRL (RA-00/0X vs CTRL P < 0.01 and RA-XX vs CTRL P < 0.01).

**Initial serum MMP-3 levels in RA patients in relation to X-ray damage at presentation**

Serum MMP-3 levels were lower in the RA-00/0X group in comparison with the RA-XX group (P < 0.01).

**Initial serum MMP-3 levels in the RA-00, RA-0X and RA-XX subgroups**

During 2 yr of follow-up, 29 of the 48 patients developed X-ray damage (≥1 Sharp point). Characteristics at study entry of the three subgroups are summarized in Table 3. There were no significant differences between the three groups in age, gender, joint pain score, joint swelling score and Ritchie articular index. CRP levels were lower in the RA-00 group (P < 0.01). In the RA-00 group (n = 19), 53% had a positive RF test, in contrast to 83% in the RA-0X group (n = 29) and 80% in the RA-XX group (n = 30) (P = 0.05).

In the RA-00 group, the serum MMP-3 levels at study entry are summarized in Fig 1 and Table 2. In CTRL, the serum MMP-3 levels were undetectable (<10.0 ng/ml) or low. In these control subjects, the serum MMP-3 levels in men were higher than those in women (P < 0.01). Sex differences were not found in the groups of OA and RA patients. No differences were found in serum MMP-3 levels between CTRL and OA patients (P = 0.19). The serum MMP-3 levels in RA patients were higher in comparison with the CTRL (RA-00/0X vs CTRL P < 0.01 and RA-XX vs CTRL P < 0.01).

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entry were lower than in the RA-XX group (P < 0.01). The difference in serum MMP-3 levels at study entry between RA-00 and RA-0X patients reached borderline significance (P = 0.05). There were no significant differences in serum MMP-3 levels at study entry between the 29 patients who developed X-ray damage (RA-0X group) compared to the 30 RA-XX patients with X-ray damage at presentation (P = 0.11).

Initial serum MMP-3 levels in relation to development of X-ray damage

In the complete group of 48 RA-00/0X patients, serum MMP-3 level at study entry correlated significantly with the total Sharp score at 6 months (r = 0.34, P = 0.02) and 12 months (r = 0.32, P = 0.03). The correlation between serum MMP-3 level at study entry and total Sharp score at 24 months reached borderline significance (r = 0.28, P = 0.05). Further separate analysis of joint space narrowing and erosions demonstrated a significant correlation between serum MMP-3 levels at study entry and joint space narrowing at 6 months (r = 0.41, P < 0.01), 12 months (r = 0.37, P < 0.01) and 24 months (r = 0.32, P = 0.03). In the subgroup of 29 RA-0X patients, there was also a significant correlation between serum MMP-3 at presentation and joint space narrowing at 6 months (r = 0.42, P = 0.02) and 12 months (r = 0.37, P = 0.04). There were no correlations between initial serum MMP-3 levels and erosions at any time point.

At a cut-off point for serum MMP-3 of 80 ng/ml (the upper limit of CTRL and OA patients), we found a positive predictive value for the development of X-ray damage within 2 yr of 91.7% (sensitivity 37.9%, specificity 94.7%).

Serum MMP-3 levels in relation to clinical parameters and CRP in the 48 patients without initial X-ray damage

Serum MMP-3 correlated with joint swelling at study entry and after 24 months. The other clinical parameters did not correlate with MMP-3 at any time point.

Serum MMP-3 levels correlated with CRP at study entry (r = 0.42, P < 0.01), 6 months (r = 0.56, P < 0.01), 12 months (r = 0.52, P < 0.01) and 24 months (r = 0.38, P < 0.01).

A logistic regression model, with X-ray damage at 6, 12, 24 months as dependent variable and MMP-3 level and/or CRP level at study entry as independent variables, reached significance for CRP levels at study entry and X-ray damage at 6 and 24 months. In the combined model of MMP-3 and CRP, MMP-3 had no additive predictive value for the explained variance of X-ray damage at these time points. Separate analysis of joint space narrowing and erosions did not influence these results.

Discussion

Research on MMPs in an early phase of RA is of interest because early identification of patients with aggressive destructive disease is important for prognostic and therapeutic reasons. Novel more aggressive therapies, including MMP inhibitors, are currently developed [34–38] and thus the need for clinically feasible means for assessing the prognosis in the individual patient is becoming more and more important.

Even though an elevated serum MMP-3 level is not unique for RA (elevated levels have also been found in patients with for example systemic lupus erythematosus, mixed connective tissue disease and psoriatic arthritis [39, 40]), it could be a specific marker of joint inflammation and destruction in RA because it is almost exclusively produced in the inflamed synovium. Recent studies showed close correlations between serum MMP-3 and disease activity in RA [39, 41]. As far as we know, there are no studies reported that link serum MMP-3 to the development of radiological damage in RA.

In the present study, we evaluated the significance of serum MMP-3 levels in relation to the development of radiological damage in early RA. Furthermore, we investigated the relationship between serum MMP-3 and CRP.

As in other studies [14, 20, 31], we found that serum MMP-3 levels were undetectable or low in normal CTRL and OA patients. In healthy male CTRL, serum MMP-3 levels appeared to be higher than in healthy female CTRL, a phenomenon which has been reported before [14, 40]. Sex differences were not found in OA patients (possibly due to the skewed distribution) nor in RA patients (possibly due to the fact that small sex differences were overruled by the massive production of MMP-3 in these patients). Further analysis of serum MMP-3 levels in normal controls with respect to gender, age and variation in time is of interest because these variables could be important in determining the cut-off point between normal and abnormal values (study in progress).

Serum MMP-3 levels in RA patients were higher than in CTRL. Initial MMP-3 levels in patients with X-ray damage at presentation (RA-XX) were higher than the levels in patients without any X-ray damage during follow-up (RA-00), but were not different from those in patients who developed X-ray damage during the study (RA-0X). In other words, a high initial serum MMP-3 level was associated with the development of radiological damage (positive predictive value for the development of X-ray damage within 2 yr of 91.7%, at a cut-off point for serum MMP-3 of 80 ng/ml).

In the group of 48 patients without initial X-ray damage (RA-00/0X), we found a significant correlation between initial serum MMP-3 levels and the development of X-ray damage which was mainly determined by joint space narrowing in the Sharp score. In the subgroup of 29 patients who developed X-ray damage during follow-up (RA-0X), there was also a significant correlation between initial serum MMP-3 levels and joint space narrowing in the Sharp score. The finding that initial serum MMP-3 levels correlate with joint space narrowing fits with the fact that the main targets of MMP-3 are localized in the matrix of cartilage, like
proteoglycans [1, 9–11], and the fact that in animal models MMP-3 was inducible and detectable in the chondrocytes in a very early phase of the arthritis [11].

Serum MMP-3 and CRP showed significant correlations at all time points. Since the production of acute-phase proteins like CRP, as well as the production of MMP-3, is stimulated by pro-inflammatory cytokines like IL-1 and TNF-α, these correlations could be expected.

Logistic regression with X-ray damage (as total Sharp score or separated into joint space narrowing or erosions) as dependent variable did not yield statistical significance when serum MMP-3 at study entry was used as independent variable, in contrast to CRP. An explanation for this finding could be the hypothesis that it takes some time to produce enough MMP-3 to be detectable in serum. Taylor et al. [19] found a higher median serum MMP-3 in patients with established RA [mean disease duration 121.5 months (s.d. 73.1)] than in those with recently diagnosed RA [mean disease duration 12.8 months (s.d. 9.0)]. They suggest that the serum MMP-3 level is affected by the amount of inflammatory tissue within the joints, which increases over the years in this condition. The disease duration in our patient groups was even shorter (see Table 1) compared to their ‘early RA group’. In this context, further analysis concerning serum MMP-3 in the early phases of RA seems of interest.

In the combined logistic regression model of MMP-3 and CRP, MMP-3 had no additive predictive value for the explained variance of X-ray damage at these time points. The fact that both CRP and MMP-3 production are stimulated by the same cytokines could be one explanation for this result.

A direct comparison between serum MMP-3 and CRP to analyse which one is the best in predicting radiological damage was not the major goal of our study. As we look at our results, serum MMP-3 is not superior to CRP. CRP is still an excellent parameter of disease activity and for monitoring the progression of radiological damage. On the other hand, the good correlation between initial serum MMP-3 and the development of radiological damage is of importance for analysing mechanical damage and the development of radiological damage, especially when specific MMP inhibitors are introduced into the treatment of RA.

In conclusion, the serum MMP-3 level seems to be an indicator for the development of radiological damage in a significant number of patients with early RA and appears to be particularly indicative of cartilage destruction. Further longitudinal analysis with multiple measurements in early RA patients seems warranted to analyse whether MMP-3 is suitable for the monitoring of disease activity and/or progression of radiological damage.

Acknowledgement

This study was supported by a grant from ‘Het Nationaal Reumafonds’, The Netherlands.

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Serum MMP-3 and radiological damage in early RA


