Synovial fluid matrix metalloproteinase-3 levels are increased in inflammatory arthritides whether erosive or not


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Abstract

Objective. To study the levels of matrix metalloproteinase-3 (MMP-3) in the knee synovial fluid (SF) of inflammatory arthropathies (rheumatoid arthritis whether erosive or not, reactive arthritis, acute crystal arthritis) and degenerative arthropathies [chronic crystal disease, osteoarthritis and (control) meniscus pathology] and to correlate them with the degree of joint destruction, local inflammatory and immune parameters and systemic markers of inflammation.

Methods. SF levels of MMP-3 (precursor, active and tissue inhibitor of MMP-bound forms), tumour necrosis factor (TNF) α, soluble TNF receptors I and II, interleukin (IL)-6 and soluble IL-6 receptor were measured by ELISA in 107 inflammatory and 53 degenerative arthropathies.

Results. MMP-3 levels in SF were (i) significantly higher in inflammatory than in degenerative arthropathies; (ii) not related to the degree of joint destruction; (iii) significantly correlated with the levels of all SF markers tested and with erythrocyte sedimentation rate and serum levels of C-reactive protein and fibrinogen.

Conclusion. Increased MMP-3 levels in SF are found in inflammatory arthropathies and are not specific for erosive joint diseases. MMP-3 in SF is therefore a potential candidate for the assessment of the inflammatory process in joints. However, the exclusive determination of the active form could indicate the degree of joint destruction.

Key words: Synovial fluid, MMP-3, Erosions, Rheumatoid arthritis, Reactive arthritis, Acute crystal arthritis.

Stromelysin-1 or matrix metalloproteinase-3 (MMP-3) is an enzyme capable of degrading many components of the extracellular matrix and has recently emerged as being of potential interest for the diagnosis and management of rheumatoid arthritis (RA). Indeed, high levels of MMP-3 have been found in the synovial fluid (SF) and in the serum of RA patients [1–10], although concentrations are at least 250-fold lower in the latter [3, 5, 7, 8]. Serum MMP-3 levels in RA are correlated with disease activity, some radiological indices, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels in both cross-sectional and longitudinal studies [3, 5–11], supporting the hypothesis that MMP-3 is a sensitive marker of the cytokine-driven local inflammation in this disease [7]. However, elevated serum levels of MMP-3 are not specific for RA or for erosive joint diseases, as they have also been found in reactive arthritis (ReA) and in gout [3, 4, 7, 10]. Furthermore, serum MMP-3 levels were not significantly different in RA patients classified as high and low eroders [12]. Elevated MMP-3 levels in SF have also been found in acute pyrophosphate arthritis [13]. The question of the relationship between SF MMP-3 and erosive status has been addressed rarely, only one work reporting no significant changes in RA SF MMP-3 in relation to the Larsen grade [14]. Therefore, the question remains whether elevated SF MMP-3 levels might relate directly to the degree of joint destruction, reflect the total catabolic effect of other MMPs [14] or simply reflect the extent of joint inflammation [15] and/or the chondrocyte and synovial fibroblast responses to the cytokines produced locally, whatever the aetiology. To test this hypothesis, we investigated the MMP-3 levels in the SF of various arthropathies: inflammatory dysimmune arthropathies such as ReA and RA, whether erosive or not; inflammatory non-immune diseases such as acute calcium pyrophosphate disease (CPPD) and gout (acute crystal arthritis); and non-inflammatory arthropathies such...
as osteoarthritis (OA), chronic CPPD and meniscus pathology. We studied MMP-3 levels in SF in relation to the degree of joint destruction and to the concentrations of molecules reflecting the underlying inflammatory or immune process: tumour necrosis factor-\(\alpha\) (TNF-\(\alpha\)), soluble TNF-receptor I (sTNF-R1), sTNF-RII, interleukin (IL)-6 and soluble IL-6 receptor (sIL-6R). MMP-3 levels in SF were also studied in relation to SF cellularity and to the classical serum markers of inflammation: ESR, CRP and fibrinogen. Our data show that MMP-3 levels in SF are elevated in all inflammatory arthropathies, whether acute or chronic and whether erosive or not, and correlate with all of the inflammatory variables tested. MMP-3 in SF is therefore a potential candidate for the assessment of the joint inflammatory process.

Patients and methods

\textit{Patient selection}

SF samples were obtained from 159 patients undergoing arthrocentesis of the knee for diagnostic or therapeutic purposes. Seventy-three samples were obtained from patients with RA, as defined by the 1987 American College of Rheumatology revised criteria [16]. All patients had clinically active synovitis at the time of arthrocentesis. Radiographs of the hands, feet and knees were obtained within 3 months before or at the time of arthrocentesis; they allowed classification into three distinct groups according to Larsen grade [17] (erosive disease of at least Larsen grade 2 in hands/feet and Larsen grade 3 in knees): (i) 13 patients without erosions in the hands, feet or knees (knee−/hand− or k−/h−); (ii) 16 patients without erosions in the aspirated knee (Larsen grade <3) but with erosions visible in their hands and/or feet (Larsen grade 2) (knee−/hand+ or k−/h+); (ii) 44 patients with erosions in the hands and/or feet (Larsen grade 2) and in the knees (Larsen grade 3) (knee+/hand+ or k+/h+). The demographic and clinical data of the patients are shown in Table 1. Patients from the first two groups (non-erosive RA and erosive k+/h+ RA) were matched for disease duration, while patients with erosive k−/h− RA had a significantly longer disease duration (Table 1). Patients with erosive RA (k−/h+ and k+/h+) were matched for positivity for rheumatoid factor (RF). SF samples were also obtained from 34 patients with inflammatory arthropathies: 23 with ReA (mean age 42.7 yr, range 19–60 yr; 11 females, 12 males) and 11 with acute crystal arthritis (CPPD and gout) (55.5 yr, 24–73 yr; three females, eight males), and from 52 patients with non-inflammatory arthropathies: nine with chronic CPPD (70.3 yr, 49–85 yr; four females, five males), 22 with OA (59.1 yr, 39–76 yr; 10 females, 12 males) and 21 undergoing opaque arthrography for meniscus pathology (28.7 yr, 14–54 yr; 12 females, nine males). All patients fulfilled the diagnostic criteria for the respective disease: ReA (seronegative oligoarthritis with cultural and/or serological evidence of either sexually transmitted disease or enteritis due to \textit{Salmonella} or \textit{Yersinia} infection) [18], OA [19] and crystal arthritis (radiological evidence of pyrophosphate deposit within the cartilage and/or identification of pyrophosphate or monosodium urate in the SF). At the time of arthrocentesis, 56 of 86 non-RA patients were taking non-steroidal anti-inflammatory drugs (NSAIDs): 10 had meniscus pathology, 10 had OA, three had chronic CPPD, 11 had acute crystal arthritis and 22 had ReA.

\textit{SF sampling: biological and immunological parameters}

SF samples were aspirated from the knee joint under aseptic conditions, and centrifuged at 2000 r.p.m. for 20 min at 4°C to remove all cells and debris. The supernatants were stored at −80°C prior to assay. Levels of TNF-\(\alpha\), sTNF-R1 (p55), sTNF-RII (p75), IL-6 and sIL-6R [Biosource Europe (formerly Medgenix), Fleurus, Belgium] in the SF were determined simultaneously by enzyme-linked immunosorbent assay (ELISA)

\begin{table}[h]
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\begin{tabular}{|l|c|c|c|}
\hline
                           & Non-erosive & Knee−/hand+ & Knee+/hand+ \\
\hline
Female/male               & 6/7         & 13/3        & 29/15        \\
\hline
Age (yr)                  & Mean ± s.e.m. & 46.8 ± 2.2 & 54.8 ± 2.2  & 60.9 ± 2.2* \\
\hline
Disease duration (yr)     & Mean (median) ± s.e.m. & 3.1 (2.5) ± 0.8 & 5.1 (2) ± 1.2 & 10.1 (7.5) ± 1.4* \\
\hline
Positive RF               & 4 (30.7)* & 11 (68.7) & 32 (72.7) & \\
\hline
Number of previous DMARDs & Mean ± s.e.m. & 1.3 ± 0.2 & 1.6 ± 0.5 & 3.2 ± 0.3* \\
\hline
Concomitant DMARD         & 6 (46) & 9 (56) & 26 (59) & \\
\hline
Concomitant methotrexate  & 4 (31) & 5 (31) & 12 (27) & \\
\hline
Other concomitant DMARD   & 2 (15) & 4 (25) & 14 (32) & \\
\hline
Concomitant corticosteroids & 3 (23) & 8 (50) & 19 (43) & \\
\hline
Prednisolone daily dose (mg) & Mean ± s.e.m. & 8.4 ± 0.8 & 8.7 ± 1.5 & 10.5 ± 1.3 \\
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Concomitant NSAIDs        & 13 (100) & 16 (100) & 44 (100) & \\
\hline
CRP (mg/l)                & Median (interquartile range) & 16 (5–21)* & 42 (23–61) & 33 (10–63) \\
ESR (mm/h)                & Median (interquartile range) & 20 (15–44) & 31 (23–61) & 49 (30–74) \\
\hline
\end{tabular}
\end{table}

\textsuperscript{*}P<0.05 vs erosive knee−/hand− RA (Mann–Whitney test for age, disease duration, number of previous DMARDs, prednisolone daily dose, ESR and CRP level; \(\chi^2\) test for all other data).

\textsuperscript{1}DMARD, disease-modifying anti-rheumatic drug; NSAID, non-steroidal anti-inflammatory drug.
using specific monoclonal antibodies and according to the manufacturer’s recommendations. SF levels of MMP-3 were measured by ELISA using a one-step sandwich method described previously [11, 20]. This assay measures both precursor and active forms of MMP-3 as well as active MMP-3 complexed with tissue inhibitors of MMPs (TIMPs) (but not with α2-macroglobulin), referred to in the text as ‘MMP-3’. No cross-reactivity was observed with other human pro-MMPs (pro-MMP-1, pro-MMP-2 and pro-MMP-9).

In an attempt to determine each of the three forms of MMP-3 measured by our ELISA, we also assessed separately pro-MMP-3 and MMP-3/TIMP-1 complexes by immunoassay (Chemicon, Temecula, CA, USA) as well as active MMP-3 by a bioactivity assay (Chemicon) in the 24 synovial fluids still available (six in each RA group and six in the OA group), according to the manufacturer’s recommendations. One unit of MMP-3 activity was defined as the amount of enzyme degrading 1 μg of substrate per minute. Sera were collected simultaneously with arthrocentesis in 94 patients (three with meniscus pathology, five with OA, three with chronic CPPD, 10 with acute crystal arthritis, 15 with ReA, 11 with k-/h− RA, 16 with k-/h+ RA and 31 with k+/h+ RA). ESR was determined by the Westergren method. Serum levels of CRP and fibrinogen were measured by nephelometry using specific antisera. SF cellularity, determined using a Coulter counter, was also determined in these patients.

**Statistical analysis**

The demographic data on the patients are expressed as mean ± s.e.m. or as totals, and were compared by the Mann–Whitney U-test and the χ² test respectively. SF variables are expressed as median values (with the 25–75% interquartile range). Between-group differences were analysed by the Mann–Whitney U-test. However, because multiple groups were compared, P values were corrected by Bonferroni’s method. For comparisons involving the eight groups, a corrected P value of 0.0017 (0.05/28) was necessary to reach significance at the 5% level. For comparisons involving the five groups of inflammatory arthropathies, a corrected P value of 0.005 (0.05/10) was necessary to reach significance at the 5% level. Correlations were sought using multiple regressions, after logarithmic transformation. P values less than 0.05 were considered significant.

**Results**

The first question we addressed was whether increased SF MMP-3 levels were specific for RA. We therefore compared SF MMP-3 levels in the various arthropathies with those in the control meniscus group. As shown in Fig. 1, SF MMP-3 levels were significantly higher in all inflammatory arthropathies, acute crystal arthritis, ReA and the three RA groups than in the control meniscus group. However, when using the more stringent criterion of Bonferroni’s correction for multiple testing, the difference between non-erosive RA and meniscus was no longer statistically significant. Within the RA population, no significant difference was found between patients according to the use of steroids or of methotrexate (data not shown). SF MMP-3 levels were similar in OA, chronic CPPD and meniscus pathology.

We then addressed the question of the relationship between SF MMP-3 and the degree of joint destruction in inflammatory arthropathies. Because the clinical analysis of the three RA subgroups showed that the erosive k-/h+ RA and non-erosive RA groups were matched for disease duration and that the erosive k+/h+ RA group had a longer disease duration (Table 1), SF MMP-3 levels were compared with those of the erosive k-/h+ RA group. SF MMP-3 levels were not

![Fig. 1. Synovial fluid MMP-3 levels in non-inflammatory and inflammatory arthropathies. Boxes represent the interquartile range, i.e. the middle 50% of the data, between the 25th and 75th quartiles. Whiskers represent the 10th and 90th quartiles, and circles represent values outside this range. *P < 0.05 compared with meniscus pathology (control) (Mann–Whitney test with Bonferroni correction); **P = 0.0088 compared with meniscus pathology (control) (Mann–Whitney test); the difference was not statistically significant with Bonferroni correction.](https://academic.oup.com/rheumatology/article-abstract/39/12/1357/1784191/Synovial-fluid-matrix-metalloproteinase-3-levels)
significantly different in the non-erosive RA, acute crystal arthritis and ReA groups compared with the erosive k-/h+ RA group, suggesting that increased SF MMP-3 levels are not specific for erosive joint diseases.

The SF of inflammatory diseases, the three RA groups, ReA and acute crystal arthritis contained higher levels of MMP-3, IL-6, TNF-α and their soluble receptors than the SF of non-inflammatory disease, OA, chronic CPPD and meniscus pathology (Table 2). Correlations were sought between SF MMP-3 and the other SF and serum variables in the entire population. Positive significant correlations were found between log MMP-3 concentration and log concentrations of all markers tested (Fig. 2 and Table 3). Of interest, strong positive correlations were found for concentrations reflecting local and systemic inflammation, SF IL-6, SF neutrophils, serum ESR and CRP. The correlations found between SF levels of MMP-3 and of the cytokines and their soluble receptors are illustrated in Fig. 2 for each arthropathy. Correlations between SF MMP-3 and the selected variables were also determined for each group separately. SF levels of MMP-3 were significantly correlated with IL-6 in both erosive RA groups (r = 0.54, P = 0.03 in the erosive k-/h+ RA group; r = 0.41, P = 0.01 in the erosive k+/h+ RA group) and with white blood cells (WBCs) and neutrophils in the erosive k+/h+ RA group (r = 0.59, P = 0.002; r = 0.69, P = 0.0001 respectively) and in the non-erosive RA group (r = 0.64, P = 0.04; r = 0.91, P = 0.0002). SF levels of MMP-3 were not correlated with those of TNF-α in any group studied separately, but they were positively correlated with sTNF-RI levels in OA (r = 0.61, P = 0.0026) and chronic CPPD (r = 0.65, P = 0.0056), and with sTNF-RII levels in OA (r = 0.46, P = 0.037), chronic CPPD (r = 0.72, P = 0.029) and erosive k+/h+ RA (r = 0.36, P = 0.023).

As observed for SF MMP-3, we failed to identify an individual SF parameter that was specific for erosive RA. Although TNF-α levels were significantly higher in the SF of both erosive RA groups than in non-erosive RA (P = 0.015 for erosive k-/h+ RA and P = 0.0052 for erosive k+/h+ RA), they did not differ significantly from those in ReA and acute crystal arthritis (Table 2). The elevated SF levels of IL-6 were not representative of RA or of its erosive capacity, as the highest levels were observed in acute crystal arthritis (Table 2).

Comparison of the two erosive RA groups, which were matched for RF but not for disease duration, demonstrated significantly higher SF levels of sTNF-RI and sTNF-RII in the k+/h+ RA group (Table 2). Therefore, the increased SF levels of the TNF-α soluble receptors seem to be specific for a longer duration of disease, because their levels were similar in the non-erosive and erosive k-/h+ groups, which were matched for shorter disease duration. They may also reflect local joint destruction, as they are evident in knees with X-ray-diagnosed erosions.

While the data suggest that the MMP-3 levels are representative of the inflammatory process rather than joint destruction, the latter is the result of the effects of the active form of MMP-3. We therefore attempted to determine separately the active, precursor and TIMP-bound forms of MMP-3 in the available OA and RA samples. As shown in Table 4, concentrations

![Fig. 2](image-url). Positive linear correlations between synovial fluid levels of MMP-3 and IL-6, TNF-α and their soluble receptors in the entire population. Each arthropathy is represented by a different colour. When calculated for each arthropathy, only a few correlations remained significant (see text).
<table>
<thead>
<tr>
<th>Table 2. Synovial fluid cytokines, soluble receptors and cellularity</th>
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<td>Non-inflammatory arthropathies</td>
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<td>TNF-α (pg/ml)</td>
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<td>sTNF-R1I (ng/ml)</td>
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<td>IL-6 (ng/ml)</td>
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<td>sIL-6R (ng/ml)</td>
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Data are medians with interquartile range in parentheses.
ND, not detectable.
*P<0.05 compared with meniscus (Mann–Whitney test with Bonferroni correction for comparisons of eight groups); **P<0.05 in comparison with erosive knee+/hand+ RA (Mann–Whitney test with Bonferroni correction for comparisons of the five inflammatory groups).
of pro-MMP-3 and MMP-3/TIMP-1 complexes were increased in both erosive RA groups compared with OA, whereas the concentration of active MMP-3 was significantly increased only in the erosive k+h+ group, i.e. in the group that exhibited X-ray-detected knee erosions.

Discussion

Our data demonstrate that increased MMP-3 levels in SF are found in inflammatory arthropathies whether acute or chronic and whether erosive or not. To the best of our knowledge, this is the first study assessing MMP-3 in the SF of degenerative, crystalline and immune arthritides and comparing SF MMP-3 with the degree of joint destruction, with SF indicators of inflammation and immune factors, and with serum markers of inflammation. An increase in SF MMP-3 in RA patients compared with OA patients [5, 7] or patients with post-traumatic injury [1] has been shown previously. Our work extends this point by showing that SF MMP-3 is also increased in acute crystal arthritis, a non-immune inflammatory arthropathy, and in ReA, a dysimmune inflammatory arthropathy, both of which are non-erosive. Furthermore, SF MMP-3 is increased in RA whether or not the disease is erosive. No difference was observed in SF MMP-3 levels in RA patients according to their treatment, confirming earlier studies measuring MMP-3 in serum [5–7, 9, 10] and SF [1, 8]. In addition, no significant differences were found within our groups when they were analysed for age, sex or eventual NSAID therapy, confirming previous studies in RA and OA [4–6, 9, 10, 21].

The relationship between MMP-3 levels and joint destruction is still debated. It has been suggested that MMP-3 levels are related to the radiological progression of RA [3, 5, 22–24]. Conversely, no significant difference in serum MMP-3 levels was observed between RA patients classified as high or low eroders [12], nor did SF MMP-3 levels correlate with the Larsen score [14]. Our data using an ELISA measuring the precursor, active and TIMP-bound forms of the enzyme showed that increased SF MMP-3 levels were found in RA whether or not it was erosive. Furthermore, MMP-3 levels were similar in the SF of RA knees with X-ray-detected erosions (erosive k+h+ RA), the SF of RA knees in patients without X-ray-detected knee erosions (but with erosions in the hands, i.e. erosive k−/h+ RA), and in the SF of ReA or acute crystal knees without any evidence of erosions. Therefore, there does not seem to be a direct correlation between the SF level of MMP-3 measured by our ELISA and the degree of joint destruction. This does not, however, rule out a role for MMP-3 in joint destruction. First, the measurement of SF MMP-3 may indicate the level of local inflammation at the time of arthrocentesis, whereas radiological scoring is a reflection of cumulative joint damage over a period of time. Secondly, MMP-3 is capable of degrading many components of the articular cartilage, and elevated levels of active MMP-3 have been observed in RA [25]. Our preliminary data evaluating each form of MMP-3 in the three RA groups in comparison with OA showed significantly increased levels of active MMP-3 only in the erosive k+h+ RA group, whereas the concentrations of both the precursor and the complexes with TIMP-1 were increased in the erosive k−/h+ and erosive k+h+ RA groups. This strongly suggests that the proenzyme form, which represents the majority of MMP-3 detected in the SF [1, 6] and is recognized by most ELISAs used [3, 5, 7], and the active form [25 and our data] do not convey the same information thus explaining the discrepancies in the literature [3, 5, 12, 22–24]. Indeed, if levels of active MMP-3 are associated with the erosive potential of RA, a link that needs to be confirmed in larger series of patients, levels of pro-MMP-3 may reflect the synovial response to inflammatory mediators within the joint [7, 21], just as CRP reflects the liver’s acute-phase response to inflammatory mediators from the joint, such as IL-6 [26–29]. Our data on SF levels rule out any controversy concerning the origin of MMP-3 in rheumatic diseases [10, 12, 15, 21].
The significant correlations found in the total population between SF MMP-3 and the inflammatory markers support the hypothesis that MMP-3 is a synovium-derived parameter reflecting local inflammation, for the following reasons: (i) the SF MMP-3 level is highly correlated with the level of locally produced IL-6 and with the number of neutrophils, both of which primarily reflect an inflammatory process [26-30]; (ii) the SF MMP-3 level is also significantly correlated with the triad ESR–CRP–fibrinogen, as is the level of IL-6 [27-29]. The significant correlations found between the SF levels of MMP-3 and those of IL-6 and neutrophils in two different groups of RA patients, one being erosive in the aspirated knee and the other being non-erosive, also support the hypothesis of a relationship between MMP-3 levels and a joint inflammatory process.

It remains reasonable to suggest that MMP-3 levels most probably reflect the TNF-α-driven inflammation of the joint. Indeed, TNF-α is a potent inducer not only of MMP-3 in synovial fibroblasts in vitro [30–32], but also of IL-6 [33], which in turn increases the IL-1-stimulated production of MMP-3 [34]. We showed that SF MMP-3 levels were correlated with SF levels of TNF-α, but also with those of its soluble receptors sTNF-R1 and sTNF-RII, which are thought to reflect the activation state of the TNF-α system [18, 35–39]. Furthermore, anti-TNF-α therapies using monoclonal antibodies reduce serum levels of MMP-3 as well as those of IL-6 and CRP in RA patients [11, 40]. Non-erosive RA is characterized not only by lower SF levels of TNF-α than erosive RA—confirming an earlier cross-sectional study [41]—but also by lower SF levels of MMP-3 and by lower serum CRP levels. However, like increased MMP-3 levels, increased SF TNF-α levels were not characteristic of RA or of its erosive potential. Nonetheless, this does not rule out a role for TNF-α in matrix degradation. Indeed, in erosive diseases there may be a local imbalance between TNF-α and its soluble receptors, which are thought to be critical in the biological outcome of TNF-α [18, 38, 42, 43], as highlighted by the observation that the highest levels of both sTNF-R1 and sTNF-RII are found in the SF of knees with X-ray-detected erosions. This RA group is also characterized by a longer disease duration; increased levels of soluble TNF receptors may thus either reflect local joint destruction or be a marker of chronic inflammation. If the activation of the TNF-α system is involved in both the increase in MMP-3 and joint destruction, increased MMP-3 levels might be correlated with the erosive capacity of RA [22–24], albeit not directly involved in the destructive process itself; this is similar to what is known for CRP [30, 44].

Although it was not within the scope of our study, the clinical value of MMP-3 determination in SF was analysed in comparison with that of SF cellularity [45] and IL-6 levels [37, 46, 47]. Inflammatory SF contains about 20 times more WBCs than non-inflammatory SF and no significant differences in WBC counts are observed between inflammatory diseases [18, 37, 38]. However, determination of the MMP-3 concentration may provide information different from that provided by the determination of SF cellularity. WBCs infiltrating the joint do not produce MMP-3 directly [13, 48 and personal data]. Their entry into the joint by chemotaxis might be regulated by mechanisms other than those controlling MMP-3 production, as shown in animal studies in which the blockade of neutrophil influx into the rabbit joint by anti-CD18 induced no change in MMP-3 levels [49]. Our data demonstrating that high levels of MMP-3 are present in ReA whereas levels of neutrophils are low also suggest that the inflammatory process is not totally reflected in the number of neutrophils in the SF. Also in favour of the determination of MMP-3 is the fact that samples can be centrifuged and stored before analysis. The determination of MMP-3 in SF in inflammatory arthritis was further compared with that of IL-6 concentration, a variable that also reflects the local inflammatory reaction [28, 37, 46, 47]. MMP-3 is easily detected because its concentration is about 1000 times higher than that of IL-6, both in degenerative and in inflammatory diseases. Mediators other than IL-6 can modify the acute-phase response [50–52], and the measurement of IL-6 in plasma or biological fluids remains difficult because of its short half-life, the presence of blocking factors and soluble receptors, and its circadian rhythm [50, 53]. Furthermore, we have recently shown that serum MMP-3 levels in RA were better correlated than IL-6 with disease activity, in both cross-sectional and longitudinal observations, and that, like CRP (but not IL-6), they were of interest for predicting the clinical outcome [20].

Taken together, our data demonstrate that MMP-3 is a synovium-derived indicator of the inflammatory process occurring in the joint and that increased SF MMP-3 levels are not specific for RA or for erosive joint diseases. Our cross-sectional data do not, however, exclude a role for MMP-3 in joint destruction because both the active and the inactive forms of the enzyme are recognized by our assay and because the deleterious consequences of a short (acute crystal, ReA) or prolonged (erosive RA) exposure of bone and cartilage to MMP-3 might be different [10, 24]. Preliminary results strongly suggest that the determination of the active form can be linked to the presence of X-ray-diagnosed erosions. The separate determination of both precursor and active forms of MMP-3 may therefore reflect different processes: inflammation for pro-MMP-3, as shown in this work, and joint destruction for active MMP-3, a role that needs to be confirmed in longitudinal prospective studies.

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