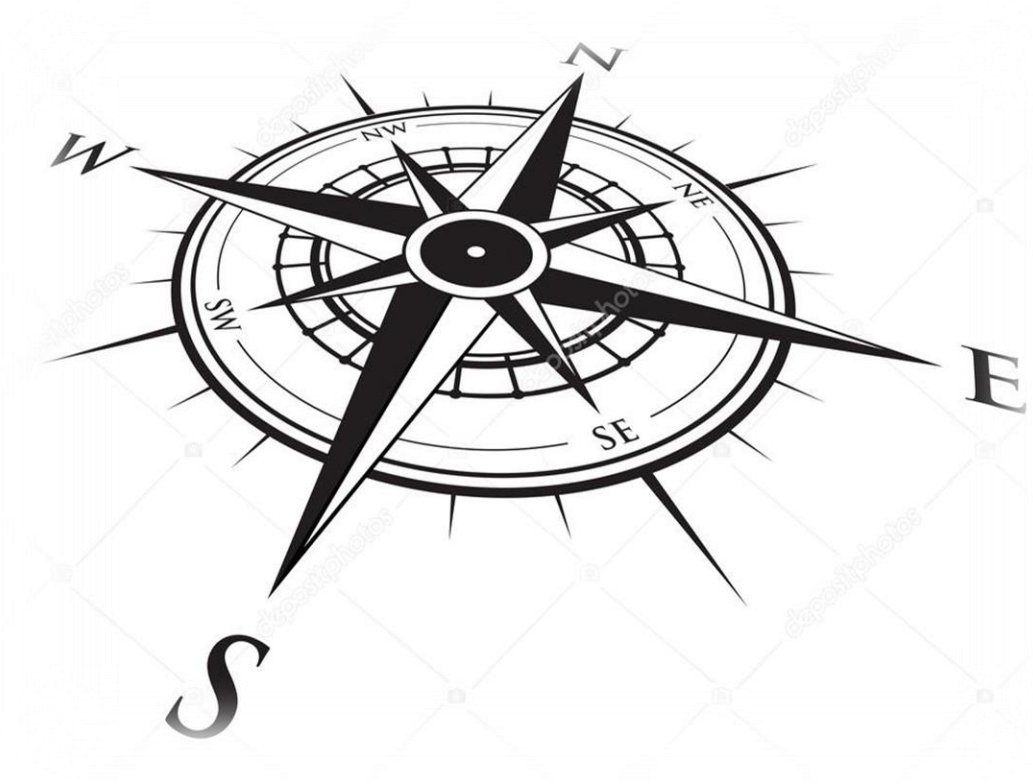
Matrix metalloproteinase-3



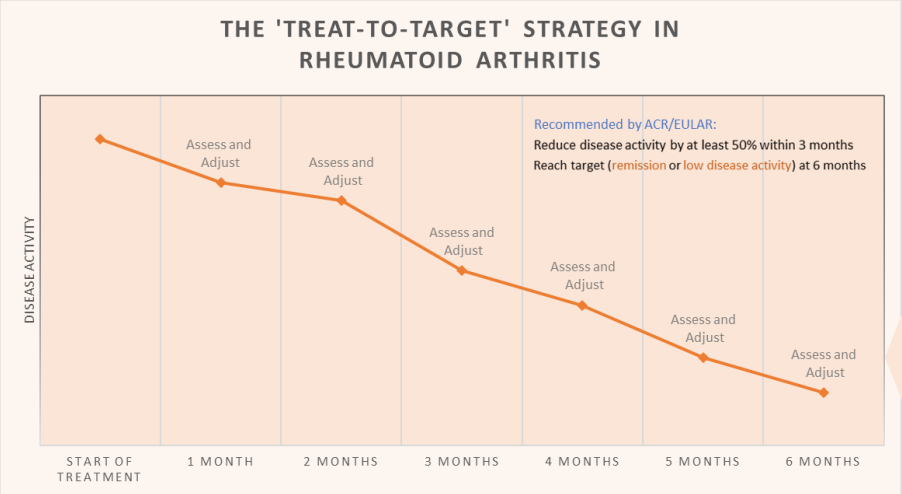
YOUR COMPASS

in tracking disease activity, assessing prognosis and therapeutic efficacy in rheumatoid arthritis

Tracking disease activity is the key in the care of rheumatoid arthritis (RA)

RA is a systemic autoimmune disease affecting about 0.5-1% of the population.[2] It is characterised by progressive, erosive and symmetrical polyarthritis and the pathological process leads to destruction of articular cartilage and bone, and may eventually result in ankylosis of the affected joints.

Over the past decades, significant progress has been made in terms of the availability of therapies and validated disease-tracking scales, as well as in terms of professional recommendations and **treat-to-target (T2) strategies.** Joint damage is irreversible, thus early and effective treatment is of paramount importance. Professional guidelines aim at achieving remission or at least low disease activity.[1,2]



Early **remission** predicts better long-term outcomes:
- improved survival
- low radiographic progression
- improved function
- essential to maintain work ability

Several tools are available to monitor disease activity and progression (e.g. DAS28, SDAI, CDAI)* that are widely used and include objective and subjective elements. Structural damage, a major determinant of disease progression, can be assessed by radiography. Several risk factors for radiographic progression are known, including high disease activity, which can be monitored by non-specific inflammatory markers such as erythrocyte sedimentation rate (We) and the C-reactive protein (CRP). However, they are not always accurate as in some cases structural damage can progress when these biomarkers are within normal levels. This suggests the need for additional, more sensitive predictive biomarkers of structural damage.[1, 2, 18]

Biomarkers can complement current practice in monitoring disease activity. The MATRIX METALLOPROTEINASE type 3 (MMP-3) could be a sensitive complement to the parameters currently being tested, it may influence clinical decision making.[1,3,6,7,18]

*DAS28: the disease activity index; SDAI: the simplified disease activity index; CDAI: clinical disease activity index

Role of MMP-3 in the pathomechanism of RA

The chronic autoimmune processes involved in the pathology of rheumatoid arthritis lead to persistent arthritis and progressive bone destruction. Matrix metalloproteinases (MMPs) play an important role in the degradation and remodelling of the extracellular matrix. MMPs are mediators of joint destruction and are detected in increased amounts in the serum, synovial fluid and membrane, and articular cartilage of RA patients.[1]

Matrix metalloproteinases (MMPs) are involved in connective tissue remodelling and are responsible for initiating degradation processes. MMP-3 is a member of the MMP family (stromelysin-1), a proteolytic enzyme produced locally in the joint, which plays an important role in RA by the formation of extracellular matrix (e.g. proteoglycans, laminin, fibronectin, or type III, IV, V, IX and XI collagens).[1,4,5] Several studies have demonstrated in RA that MMP-3 levels are elevated in the joint, in the blood, and indicate arthritic inflammatory activity.[19,20,21]

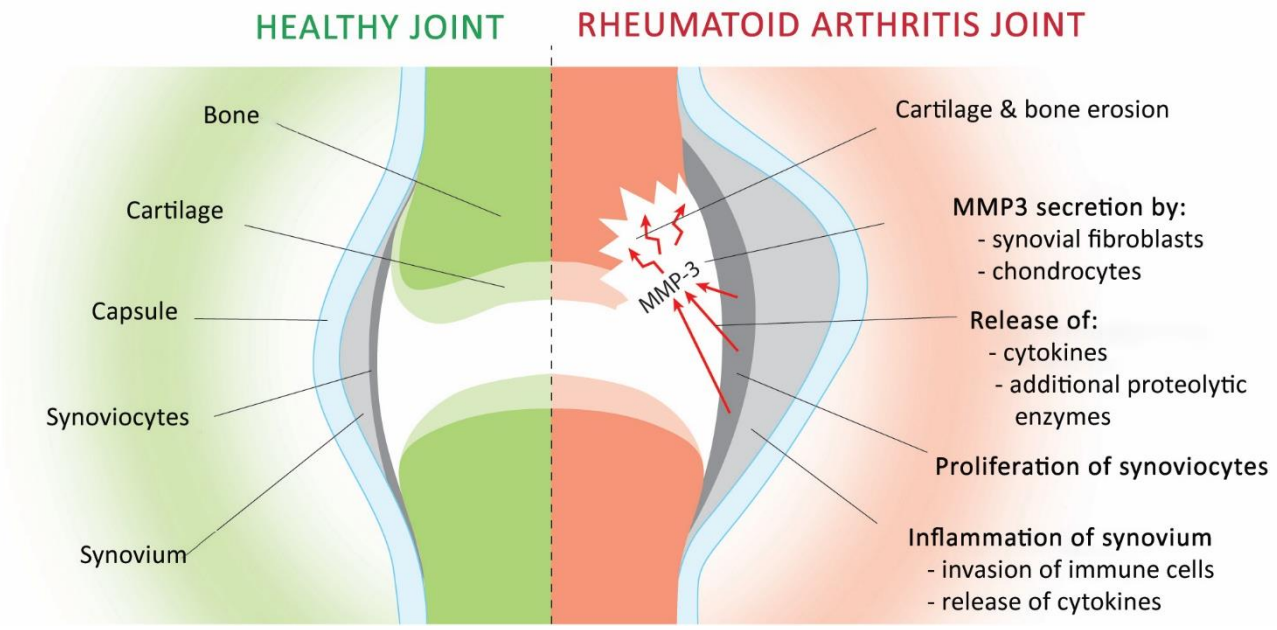


Figure 2: Role of MMP-3 in healthy and rheumatoid arthritis joints (adapted from reference [1])

Over the past decades, many studies have been published and thousands of patients have been included to investigate the role of MMP-3 as a potential biomarker, and there are countries where MMP-3 level monitoring has become part of the monitoring protocol. It has been **a mandatory element of clinical practice in Japan for more than 10 years**. [17] According to these studies and publications:

MMP-3 could predict disease activity and joint destruction. It can augment current diagnostic tools and improve the accuracy of clinical diagnosis and optimise therapeutic decisions.[1,3,7,9,11,13,18]

Serum MMP-3 correlates with disease activity [3,4,5,6]

Several studies support a role for MMPs in the pathophysiology of RA and have concluded that MMP-3 is a reliable serological marker for RA disease activity. [2,3,4,5]

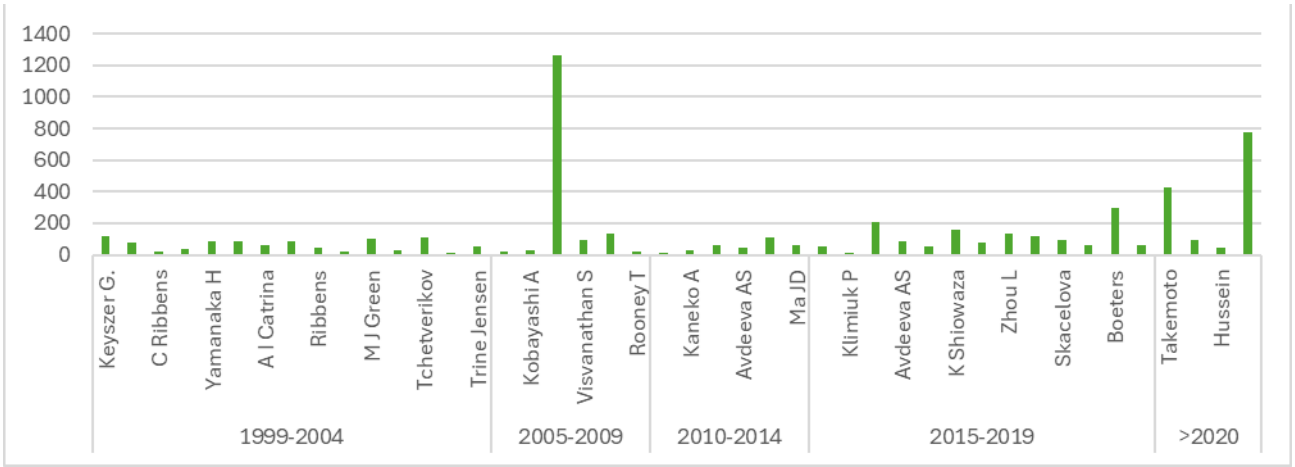
POTENTIAL AREAS OF ITS USE:

- MMP-3 can support early diagnosis and differential diagnosis
  - Being an early and reliable marker of disease activity, MMP3 determination offers early and accurate staging of the disease[6,12]
  - Elevated levels of MMP-3 in ACPA seronegative RA may support diagnosis of RA [1,8,22,23,24]
- Assessing the degree of arthritis and destruction [1, 3,6,7,9,10,11,13,19,21,22]
  - Proven correlation with radiological progression [6, 9,10,18,25]
  - Assessment of articular cartilage and non-inflammatory bone destruction. [3,6,26]
- Early identification of patients with poor prognosis [3,9,11,18,24,25,28]
- Predicting therapeutic efficacy [6,10,11,13,28]

Serum levels of MMP-3 correlate with disease activity, reflect joint and bone erosion and predict radiological progression;

and can predict the effectiveness of therapies in patients with rheumatoid arthritis[6,7]

List of major studies and publications of MMP3, based on publication date, author and number of involved patients



With the involvement of more than 5.500 RA patients

Figure 3 List of major studies and publications based on a systematic literature search

Serum levels of MMP-3 can be helpful in assessing prognosis.[3,4,5,6]

Supporting early diagnosis

MMP-3 can be elevated **early in RA** (**symptoms < 1 year**) and tends to increase with disease progression. MMP-3 levels have been shown to predict worse prognosis and correlate with Larsen score in patients without joint erosion. In a study by *Martina and colleagues*, MMP-3 levels in RA patients were significantly higher than in healthy controls and were **positively correlated with ESR, CRP, DAS28-3 and anti-CCP**. *Hu et al.* also confirmed that in early RA patients with normal CRP and/or ESR, the positivity rate of serum MMP-3 was higher than that of CRP and ESR, and that it was positively correlated with CRP levels [8]

Liang and colleagues, in a 2022 study involving 145 patients, investigated differences in lymphocyte and CD4+ T-cell subtypes between ACPA-positive and negative RA patients and evaluated the diagnostic and disease activity prognostic role of MMP-3 in ACPA-negative RA patients. ACPA negativity may occur in up to 30% of patients. Delay in diagnosis may suspend the initiation of therapy, leading to irreversible joint damage. *It has been demonstrated that in these patients, monitoring MMP-3 levels is of paramount importance and thus a tool for early diagnosis. It was also an important index for the disease evaluation, stratification of disease activity, and prediction of clinical progression in ACPA$^-$ RA patients* [8]

Proven correlation with radiological progression

It was described as early as 2000 that serum MMP-3 level may be an indicator of the development of radiological damage in patients with early RA and predict cartilage damage. This was later confirmed by several studies. [9]

Rajalingham and colleagues found that the mean serum MMP level in RA patients with radiographic joint erosion was significantly higher than in patients without erosion. Similarly, patients with significant functional impairment (HAQ-DI ≥1) had significantly higher mean MMP-3 levels compared with RA patients without significant disability. ***Serum MMP-3 is a potential biomarker and prognostic factor for radiographic joint damage and functional disability in RA*.** [29]

Houseman et al. demonstrated an association between MMP-3 and 2-year radiological progression in patients with RA. In this study carried out in 2012 showed that measuring **baseline serum MMP-3 levels increase the predictive value of anti-CCP in determining long-term radiological outcome**. The study was then extended to 8 years, which supported the long-term persistence of this predictive value. These results support the idea that MMP-3 influences pathological processes other than anti-CCP, which are essential for the development of radiological progression.[10]

It can be an indicator of remission and can also be a clue in predicting a poor prognosis

The prediction of remission and expected therapeutic success is as important in clinical practice as the assessment of an unfavourable prognosis. Several clinical trials have been conducted and have clearly demonstrated the usefulness of MMP-3.

Hattori and his team analysed data from more than 1300 patients in clinical practice and investigated the applicability of serum MMP-3 compared to other markers. They found that MMP-3 measurement was a more effective predictive marker for clinical remission (SDAI≤ 3.3) and maintenance of normal function (HAQDI≤ 0.5) than CRP values. It was concluded that MMP-3 measurement in combination with CRP or other parameters of disease activity should be used to assess clinical remission. [11]

Houseman et al. supported the long-term persistence of predictive potential with their 8-year extended study. The combined assessment of biomarkers of joint damage, such as baseline MMP-3, existing serological markers, and clinical measures may **provide important prognostic information for patients with early RA**. This finding is consistent with the conclusions of other studies. [3,7,12]

MMP-3 in predicting therapeutic efficacy

In the area of personalised medicine, the tailoring of the most effective therapy is of high importance. Additionally, cost effectiveness is no less important and also supports treatment optimisation (changing or discontinuing a therapy). In this regard, several studies have explored the place of MMP-3 in therapeutic response prediction. In 2018, *Lerner* et al. concluded in their literature review that decreased serum MMP-3 levels and mRNA MMP-3 expression in synovial fibroblasts and peripheral mononuclear cells reflect therapeutic response and their low values predict therapeutic success.[6]

According to *Takemoto* 'improvement in MMP-3 levels is key to predicting the clinical efficacy of therapy. Closer attention paid not only to major clinical indices, but also changes in MMP-3 levels, could improve our ability to optimise clinical results when treating bio-switch patients'. [13]

The mirroring of the drug responsiveness can guide treatment optimisation, thus treating to target efficiently, saving unwarranted side effects, and improving cost-effectiveness.[6]

MMP-3 shows a positive correlation with disease activity,
predict the prognosis of the disease
and therapeutic efficacy in RA patients.

Monitoring serum MMP-3 levels is simple

Features:

- Blood collection required
- Non-fasting, no preparation required by the patient
- Result can be within 1 day (lab measurement time: ~10 minutes)

The interpretation of results should be made by a physician and include a discussion of the evidence gathered, i.e. patient history, clinical examinations and other lab tests.

Test sites

MMP-3 level measurement is currently available by individual fund.

The list of measurement sites is constantly growing, with the possibility to join additional sites. For more information, please contact our office via the below availabilities!

Brief description of the product, test principle

Latex particle-sensitised immuno-turbidimetric reagent for the quantification of MMP-3 (Matrix Metalloproteinase-3) for photometric systems. Non-radioactive immunoassay based on antigen-antibody interaction (based on protein binding and electrostatic interaction).

Manufacturer name and registered office: BIOXOL Kft. (1155 Budapest, Wysocki utca 1.; Hungary)

European distributor: Auxiliis Pharma Kft (1037 Budapest, Bokor utca 15-21. 2. floor 32.)

CE registration number (OGYÉI): EN/CA01/12954/22

For more information please visit www.mmp3.hu

List of Publications

1. Szekanecz Z, Nagy G (2024): The role of matrix metalloproteinase 3 (MMP-3) in rheumatoid arthritis. Immunological Review, 2024 Vol. XVI, No. 4 pp 15-19.
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