Best Practice & Research Clinical Rheumatology 32 (2018) 550–562

Contents lists available at ScienceDirect

Best Practice & Research Clinical Rheumatology

journal homepage: www.elsevierhealth.com/berh

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MMP3 is a reliable marker for disease activity, radiological monitoring, disease outcome predictability, and therapeutic response in rheumatoid arthritis

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Keywords:
MMP3
Rheumatoid arthritis
Diagnosis
Monitoring
Activity
Responsiveness

A B S T R A C T

Matrix metalloproteinase-3 or MMP3 also known as stromelysin-1 is an enzyme that is actively involved in joint destruction in rheumatoid arthritis (RA) patients. Screening the last three decades, it appears that serum levels of MMP3 reflect positively RA disease activity, joint and bone injury, and radiological erosion and predict disease outcome and drug responsiveness as summarized in several publications reporting outcomes on more than 8000 patients with RA. MMP-3 monitoring should be embedded in the routine assessment and accompany therapeutic modalities, in personalized medical RA management.

Introduction

Rheumatoid arthritis (RA) is a long-term autoimmune disorder that primarily affects joints. It typically results in warm, swollen, and painful joints. Pain and stiffness often worsen following rest. Morning stiffness is one of the classical presentation. Most commonly, the wrists and hands are involved, with the same joints typically involved bilaterally. It runs a heterogeneous course and

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https://doi.org/10.1016/j.berh.2019.01.006
1521-6942/

various pathogenic mechanisms resulting in common symptoms and phenotype. The disease can also affect other parts of the body, and multiple extra joint presentations are described in the literature. The triplet of a persistent synovitis, systemic inflammation, and autoantibodies characterizes the disease [1].

No doubt that the first essential step toward optimizing the therapy and the long-term prognosis is early diagnosis of the disease. One of the means to differentiate between RA and multiple other entities that affect the joints is the serological marker. In fact, newly diagnosed RA is an eminently treatable disease with prospects of remission for more than half of those affected, and early diagnosis is a precondition for successful treatment [1,2]. After the medical story and joint findings, antibody results carry the greatest weight for the diagnosis. It is desirable that such a marker will also reliably predict disease development and progression. In daily clinical practice, determination of one antibody, rheumatoid factor (RF), or antibodies against cyclic citrullinated peptide (anti-CCP or ACPA) is sufficient to suspect the cause of the joint manifestations [2].

However, multiple false positive and negative exist for RF in RA, and it is generally considered as quite sensitive, albeit poorly specific for RA diagnosis [3]. It is false positive mainly in infectious diseases (malaria, HIV, toxoplasmosis, syphilis etc.) and induces false positive laboratory results (thyroglobulin, α feto protein, sex hormones binding proteins, troponin 1, various cytokines, HBV + HCV serology, and latex agglutination). Even in autoimmune diseases, it may affect autoantibodies levels (anti cardiolipin and anti β2 glycoprotein1). RF occurs in 60–80% of established and 50–60% of early RA; it reflects disease activity but is less useful in patient's diagnosis. In fact, only 11–20% with musculoskeletal complains and RF + will finally have RA [4]. Analyzing 50 studies of RF, by a meta-analysis, looking at primary and secondary care populations, RF sensitivity of 69% and specificity of 85% were found in RA [5].

ACPA is a much recent serological marker. It is an autoantibody against a citrullinated protein that was post translationally modified by peptidyl arginine deiminase, turning it from naive protein to immunogenic and pathogenic one [6]. ACPA has similar sensitivity to RF but improved specificity [7]. In the same meta-analysis mention above, including 37 studies, pooled sensitivity of ACPA was 67% and specificity was 95% [5]. However, false±ACPA results exist mainly in inflammatory and autoimmune diseases, and ACPA negative RA is well described. Based on contrasting genetic setups in ACPA positive and ACPA negative RA patients, most probably these are two distinct disease subsets, with different underlying etiologies and pathogenesis [8].

At list in primary care, no evidence is currently available to use RF or ACPA as diagnostic markers of RA, especially when low pre-test probability exists [9,10].

In academics, hospital, or rheumatology care centers, where a higher pre-test probability exist, the indications to use those serological markers are stronger. In fact, in 2010, the 2010 ACR/EULAR Rheumatoid Arthritis Classification Criteria were introduced [11]. A score of 6 or greater unequivocally classifies a person with a diagnosis of RA. The serological markers, imbedded in this classification, include maximum 3 points out of 10, were: negative RF and negative ACPA give 0 points, low-positive RF or low-positive ACPA gives 2 points, and high-positive RF or high-positive ACPA gives 3 points.

The enzyme matrix metalloproteinase-3 (MMP3), also known as Stromelysin-1, in humans is encoded by the MMP3 gene that is part of a cluster of MMP genes, localized to chromosome 11q22.3. Proteins of the MMP family are involved in the breakdown of extracellular matrix proteins during tissue remodeling in normal physiological processes, such as embryonic development and reproduction, as well as in disease processes, such as arthritis and tumor metastasis. Most MMPs are secreted as inactive pre-proteins that are activated when cleaved by extracellular proteinases. MMP3 is a proteinase synthesized and secreted by synovial fibroblasts and chondrocytes in the joints. It is actively involved in joint destruction in RA patients (Fig. 1). The MMP3 enzyme degrades collagen types II, III, IV, IX and X, proteoglycans, fibronectin, laminin, and elastin. In addition, MMP3 can also activate other MMPs such as MMP-1, MMP-7, and MMP-9, rendering MMP3 crucial in connective tissue remodeling [12,13].

While screening for serological markers in RA, it appeared that MMP3 was extensively studied in disease activity reflection, monitoring progress, and therapeutic responsiveness but did not gain enough attention by the professionals. Therefore, the subject of this review is MMP3 in RA. The aim is

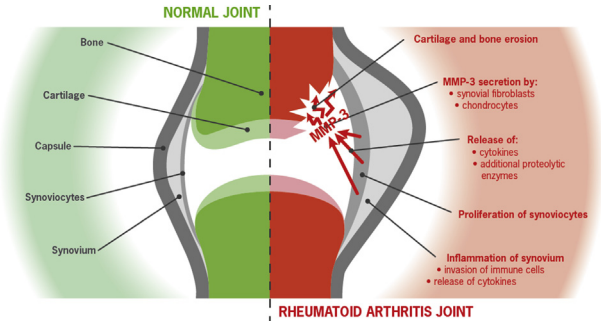

Fig. 1. Schematic presentation of an arthritic/normal joint highlighting the central role of MMP3 in joint inflammation and destruction in RA patients.

to update on MMP3 in RA and explore its place in RA disease predictability, activity monitoring, and response to various therapeutic modalities.

Material and methods

MMP3 was first sequenced in 1988 [14], which is the reason why the present search covers the period 1990–2018. Research studies, reviews, and case control series are included, while case reports are excluded from this review. Literature search strategies were performed using PubMed, Medline, EMBASE, Scopus, and the Cochrane Database of Systematic Reviews, to identify the most relevant publications.

The following search algorithm was used: ("matrix metalloproteinase-3 or "MMP3") AND ("rheumatoid arthritis or RA). The search was limited to articles or abstracts published in English. Eighty-three publications were identified. When relevant, screened titles and abstracts were selected for full text review.

Ethics: as primary data were not collected, ethical approval is not mandatory.

MMP3 in diagnosing rheumatoid arthritis

Despite the acceptable diagnostic value of ACPAs and RFs, there is still a need to unravel additional markers to further ameliorate RA diagnosis. One of those is MMP-3. In this regards, several recent reviews on biomarkers of RA did not even mention MMP3 [15–19]. However, since the introduction of the multiple-biomarker disease activity (MBDA) for RA in 2016 [20], more objective indices have been introduced, thus increasing the subjectivity in conventional indices. The MBDA comprises 12 serum biomarkers (VCAM-1, EGF, VEGF-A, IL-6, TNFRI, YKL-40, MMP-1, MMP-3, leptin, resistin, SAA, and CRP) and was lately shown to reflect disease activity and predict radiological progression and the risk of flare after drug reduction [20]. It is difficult to allocate MMP-3 to its differential value in RA diagnosis, facing 12 biomarkers, and for this reason, following are studies that explore separately MMP-3 with respect to its diagnostic value in RA. Degradation of the joint cartilage is caused in RA by proteinases derived from inflamed synovium and stimulated chondrocyte. Both in vitro and in vivo studies indicate that synovial fibroblasts or B cells are producers of MMP-3 [21,22]. It is involved in the pannus invasion and cartilage degradation [23] and plays an important role in connective tissue destruction through the activation of procollagenase, in addition to its direct effect on extracellular matrix components [24]. Its important role in RA pathogenesis is reflected by its levels in the inflamed synovial fluid [25], and multiple groups reported its systemic levels having diagnostic value as a laboratory marker of RA [25–30]. When correlating RA synovitis histology to serum MMP-3 level, Ma et al., 2014 concluded that its systemic levels reflect significantly the histological grade, score, and activation of synovial stromal sub score [30]. However, controversies exist on MMP-3 as a diagnostic marker of RA. Despite the fact that elevated MMP-s

levels reflected disease activity of RA better than cytokine levels or connective tissue turnover markers, it did not exceed the association of CRP with clinical activity [31,32]. When compared to multiple RA laboratory markers, Shoenfeld's group found that elevated anti-CCP had better diagnostic performance than MMP-3 [33]. Comparing to MMP-1, MMP-3 levels were not higher in RA patients than those in non-RA patients [34]. It can be summarized that MMP-3 is important in RA development and joint erosions progression but does not exceed the diagnostic performances of the ACPAs or other serum markers, in the diagnosis of RA.

MMP3 in monitoring rheumatoid arthritis disease activity

In the correlation to RA disease activity, the place of MMP-3 stands stronger than its diagnostic capacity. Screening the literature of the last 28 years, the majority of the studies concluded that MMP-3 is a reliable serological marker for RA disease activity [31,32,35–52]. Table 1 summarizes serum MMP-3 positive reflection of different clinical and laboratory aspects of RA disease activity, chronologically. It can be seen that serum MMP-3 correlates positively with CRP, ESR, Das28, synovial inflammatory parameters, swollen and painful joints, pro-inflammatory cytokines, health assessment questionnaire, cartilage damage, and ultrasonic appearance.

MMP3 in evaluating rheumatoid arthritis radiographic progression

MMP3 is a key factor in bone resorption in RA pathomechanism, where it mediates the removal of the outer osteoid layer, facilitating the close attachment of the osteoclasts to execute the underlying bone damage. It is part of the proteinase or components of the extracellular matrix of bone and cartilage family such as CTX-I, CTX-II, COMP, TIMP1, PYD, RANK/OPG, and CXCL13 [53]. Its production is up regulated by the classical pro-inflammatory cytokines: IL-1β, TNF, and IL-17A, and by its mediator of synthesis, the acute phase reactant serum amyloid A. IL-4 and IL-13, however, down regulate MMP3 levels [46]. Notably, the severity of RA can be assessed objectively by radiographic progression. Being a significant effector in cartilage metabolism and actively involved in cartilage destruction, not

Table 1
A chronological summary of serum MMP-3 positive reflection of different clinical and laboratory aspects of RA disease activity.

Parameter of RA disease activity	Correlation to MMP-3	No of RA patients	Year published	Reference
CRP, Lansbury's activity index, SJC, painful joint count	+	60	1998	[35]
Clinical disease activity	+	115	1999	[31]
SJC, ESR, CRP, DAS	+	33	2000	[36]
CRP, IL-6, DAS		20	2000	[37]
CRP, Larsen score, DeltaHAQ	+	98	2003	[38]
Pro-MMP-3: DAS, sharp score	+	109	2003	[39]
CRP, cytokines, SJC, disease activity, synovial fluid MMP-3	+	22	2005	[32]
synovial fluid MMP-3, synovial inflammatory cell infiltration score	+	29	2007	[40]
ESR, CRP, Larsen score	−	85	2007	[41]
IL-8, IL-1β, CRP	+	144	2007	[42]
CRP, COMP, DAS28,	+	98	2009	[43]
IL-6, MMP1, TIMP-1	+	22	2010	[44]
IL-8, IL-6, IFNϒ, VEGF, COMP, CRP, SAA	+	128	2013	[46]
Human synovial membrane culture, CRP, ESR	+	47	2014	[47]
Lansbury articular index, disease activity	+	100	2014	[48]
CRP, ESR, SAA, DAS28, SJC,	+	206	2015	[49]
Albumin-thiol redox state, CRP, DAS28	+	47	2015	[50]
US7, DAS28, deltaHAQ	+	133	2016	[51]
CRP, DAS28, anti-CCP, ESR, radiographic stage	+	92	2017	[52]

DAS-Disease activity score, SJC-Swollen joint count, DeltaHAQ-health assessment questionnaire, Cartilage oligomeric matrix protein-COMP, VEGF-Vascular endothelial growth factor, SAA-Serum amyloid A, US7-Ultrasonic 7 joints score, and TIMP-1-Tissue inhibitor of metalloproteinase 1.

Table 2
A chronological summary of serum MMP-3 positive reflection of different radiological damage scoring.

Parameter of radiological damage in RA	Correlation to MMP-3	No of RA patients	Year published	Reference
X-ray	+	78	1999	[54]
Joint space narrowing, Sharp score	+	33	2000	[36]
X-ray of hands and feet, Larsen method	+ pro-MMP3	337	2000	[55]
X-ray of hands and feet, Larsen method	+	82	2000	[56]
X-ray of hands and feet at presentation	+	85	2001	[34]
X-ray, Sharp/Van der Heijde methods	+ MMP-3 6A/6A promoter genotype	103	2002	[57]
X-ray of hands and feet, Larsen method	+	98	2003	[38]
Swollen joint count, Sharp/Van der Heijde methods	+	32	2003	[58]
X-ray of hands, MRI, DXR-BMD	+	72	2004	[59]
X-ray, Larsen score	+ MMP3 6A/6A promoter genotype	254	2004	[60]
X-ray, Ratingen score	+ MMP3 5A/6A promoter genotype	308	2004	[61]
X-ray by modified Larsen method	+	132	2007	[62]
X-ray of hands, Sharp/Van der Heijde/ Steinbrocker methods	+5A/6A promoter polymorphism of MMP3	128	2007	[63]
X-ray, Sharp/Van der Heijde methods	+	58	2012	[64]
X-ray hand/wrist, Sharp score	+	56	2015	[65]
X-ray, modified total Sharp score, joint space narrowing	+	244	2016	[66]
X-ray hands and distal feet	+	87	2016	[67]

DXR-BMD-digital x-ray radiogrammetry, MRI-magnetic resonance imaging.

surprisingly, MMP3 became a prime candidate to reflect the cartilage destruction and bone erosion in RA patients, as reflected by radiological assessment. Table 2 summarizes chronologically the studies that established serum MMP3 levels as a good biomarker for cartilage degradation and radiological damage progression.

Several studies appreciated MMP levels as a good marker in early RA, as assessed radiologically [34,36,38,54,56,65,67], while others, later in the disease course, along the disease progression [55–61,66,67].

Table 2 summarized only radiological evaluation by X-rays, but cartilage damage and bone erosion were extensively assessed by ultrasound [48,51,53,68] and less frequently by Joint's MRI [43,53,69–71] and seldom by F-FDG-PET scan [69]. In all of those imaging modalities, MMP3 reflected cartilage damage and bone erosions. Recently, it was found that the combination of MMP3 and ultrasonography (US7) does not add to the diagnosis and to the efficacy to monitor RA disease activity. MMP3 determination alone is sufficient [51]. Interesting is the follow-up study [65] done by Chen LF from Guangzhou, China, showing that serum MMP-3 normalization may be a potential predictor for less than one-year radiographic progression in RA (Prof. Lie Dai, unpublished, personal communication).

MMP3 as predictive factor in RA diagnosis, progression and outcome

Following the current recommendations, i.e., RA diagnosis, treatment and follow up decision-making are based on diagnostic biomarkers, disease activity, and therapy adjustment to treat to target, aiming to reach remission or suppress activity with the ultimate goal to avoid joint damage and prevent radiological progression. One of the major desire is to offer a reliable predictor that could help in the diagnosis, therapeutic decision, clinical and imaging follow-up and personal prognosis, along with disease progression and remission.

Table 3
A chronological summary of serum MMP-3 as a predictive marker for disease activity, joint and bone damage, and disease outcome in RA patient.

Prognostic parameter	MMPs	No of RA patients	Publication year	Reference
Joint destruction	+	82	2000	[56]
Disease outcome	+	20	2000	[37]
Joint destruction	+	review	2002	[29]
Joint damage	+ pro-MMP3	109	2003	[39]
Progression of erosive disease	+ MMP1	98	2003	[38]
Disease outcome	MMP-3 6A/6A genotype	254	2004	[60]
Radiographic progression	+ CTX-II	132	2007	[62]
Radiographic progression	MMP-3 6A/6A genotype	128	2007	[63]
Long-term disability	+ RF	1265	2007	[72]
Joint destruction	+	review	2010	[28]
Radiographic progression	+	58	2012	[64]
Diagnostic prediction	+ hsCRP	44	2013	[73]
Radiographic progression	+	56	2015	[65]
Disease activity, Joint damage	+	81	2016	[71]
Articular destruction	+	87	2016	[67]

CTX-II: C-telopeptide of type II collagen, RF: rheumatoid factor, and hsCRP: high-sensitivity C reactive protein.

In fact, several predictor variables were explored in RA patients. Prognostic biomarkers for disease activity, radiographic progression, diagnostic prediction, long-term disability, and disease outcome are some of them. The following Table 3 summarizes chronologically the literature on MMP3 as a predictor of those prognostic parameters. The subject of therapeutic prediction will be dealt separately in the next paragraph.

MMP3 as a biomarker for drug responsiveness in rheumatoid arthritis

In the area of personalized medicine, the tailoring of the most effective therapy is of paramount importance. More so, in the area of cost effectiveness, no less important is the correct decision to stop the treatment when failed. In this regards, several studies explored the place of MMP3 in monitoring therapy success and predict therapy failure. Table 4 summarizes those studies.

It can be deduced that decreased serum MMP3 levels and mRNA MMP3 expression in synovial fibroblast and peripheral mononuclear cells reflect various drug's responsiveness, and those decreases are predictive of therapeutic success. However, sustained high levels along the therapy (MMPs at week 54 on infliximab, ref 66) predict treatment failure.

Discussion

Contrary to the 1987 American College of Rheumatology criteria, the 2010 ACR/EULAR classification criteria for RA [92] were formulated to recognize earlier stage of the disease, thus identifying patients at risk of developing persistent and erosive arthritis. Since 2010, multiple re-evaluations of the performance of the 2010 criteria were done. The results having a wide range of differences and controversies ranging from praising [93–96] to criticizing [97–102] and even concluding not adding to the 1987 criteria [97,102]. The 2010 criteria allow earlier diagnosis but may falsely diagnose self-limited or undifferentiated arthropathies [94,95,98,99,101]. One of the 2010 criteria is serological abnormalities, and up till now, RF and ACCP are the most frequently performed. The present review describes the beneficial information that can be drawn from serum MMPs determination. Despite the fact that it does not outperform the ACCP contribution to RA diagnosis, MMP3 offers substantial information, and as it correlates positively with disease activity, it reflects reliably various radiological damage scorings, correlates to joint and bone damage, predicts disease outcome, and is a predictive marker for therapeutic drug responsiveness, in RA patients. Another aspect that stood out while screening the literature

Table 4
A chronological summary of serum MMP-3 as a predictive marker for therapeutic drug responsiveness in RA patients.

Therapeutic success monitoring	Mode of therapy	Publication year	No of RA patients	Reference
Serum MMP3 decrease	anti TNFα cA2	1997	?	[74]
Serum MMP3 decrease	anti TNFα (etanercept)	2002	60	[75]
Serum MMP3 decrease	SSZ or SSZ + MTX	2002	82	[76]
Serum MMP3 decrease	IFX or IFX + MTX	2004	14	[77]
Serum MMP3 decrease	leflunomide in resistant RA	2006	30	[78]
Serum MMP3 decrease	IFX + MTX or MTX	2007	96	[42]
Serum MMP3 decrease	tocilizumab (anti IL-6)	2009	22	[79]
Serum MMP3 decrease	etanercept	2010	45	[80]
Synovial MMP3 inhibition	adalimumab + MTX	2011	5	[81]
DAS28 + MMP3+ driven therapy group achieved remission	SSZ + MTX + biological agents	2011	61	[82]
Serum MMP3 decrease	toclizumab (anti IL-6)	2012	31	[83]
MMP3 mRNA decrease in peripheral mononuclear cells	IFX	2012	30	[84]
Serum MMP3 decrease	TNF antagonist + MTX	2013	109	[85]
Serum MMP3 decrease	tocilizumab	2013	42	[86]
Serum active form of MMP3 decrease	anti TNFα	2014	47	[47]
Serum MMP3 decrease	MTX or MTX + IFX	2015	206	[49]
Serum MMP3 decrease	rituximab (anti $CD20^{+}$ B cells)	2015	12	[87]
MMP3 mRNA decrease in synovial fibroblasts	iguratimd (T-614)	2015	?	[88]
Serum MMP3 decrease	MTX	2016	161	[89]
Serum active MMP3	Tocilizumab + MTX	2018	741	[90]
Serum MMp3	adalimumab	2018	114	[91]

SSZ: sulfasalazine, MTX: methotrexate, and IFX: infliximab.

is the MMP3 surge, in early stages of RA [34,36,38,54,56,65,67], thus going along with the 2010 criteria aims for early stage diagnosis, early disease modifying anti-rheumatic initiation, and potential prevention of definitive skeletal and articular damage [92,93].

It appears that the MMP3 was extensively explored in RA but did not gained enough attention by the rheumatological societies. It is suggested that when the 2012 RA classification criteria will be revised, MMP3 should be introduced. Fig. 2 describes the suggested MMP3-driven flow chart, based on its differential levels: normal, elevated, or high titers. Interestingly, MMP-3 levels are associated with nonarticular complications of RA, of which pulmonary artery systolic pressure [103] and renal dysfunction [104] are some recent examples, probably reflecting the underlying systemic inflammation.

Several clinical and cost-effective benefits arise from using MMP3 in clinical practice, aiming for early diagnosis, early treat to target therapy and prevent definitive erosions and damage:

1 Being an early and reliable marker of disease activity, MMP3 determination offers early and accurate staging of the disease.
2 As reflecting joint and bone damage, it can lower down the number of repeated irradiations and decrease the diagnostic as well as the follow-up detrimental health side effects and the economic burden.
3 The mirroring of the drug responsiveness or failure can guide the medical team to continue or stop a certain therapeutical protocol, thus treating to target efficiently, saving unwarranted side effects, and improving cost-effectiveness.
4 Serial MMP3 determination, along the course of the disease, is going along with the modern implementation of personalized medical treatment, for the patient benefit.

Finally, when studied in RA patients with Hashimoto's thyroiditis, serum MMP3 levels were significantly correlated to the thyroid inflammation and destruction [105]. The study opens up a new aspect of potential MMP3 reflection of extra articular, nonskeletal organ injury associated with RA.

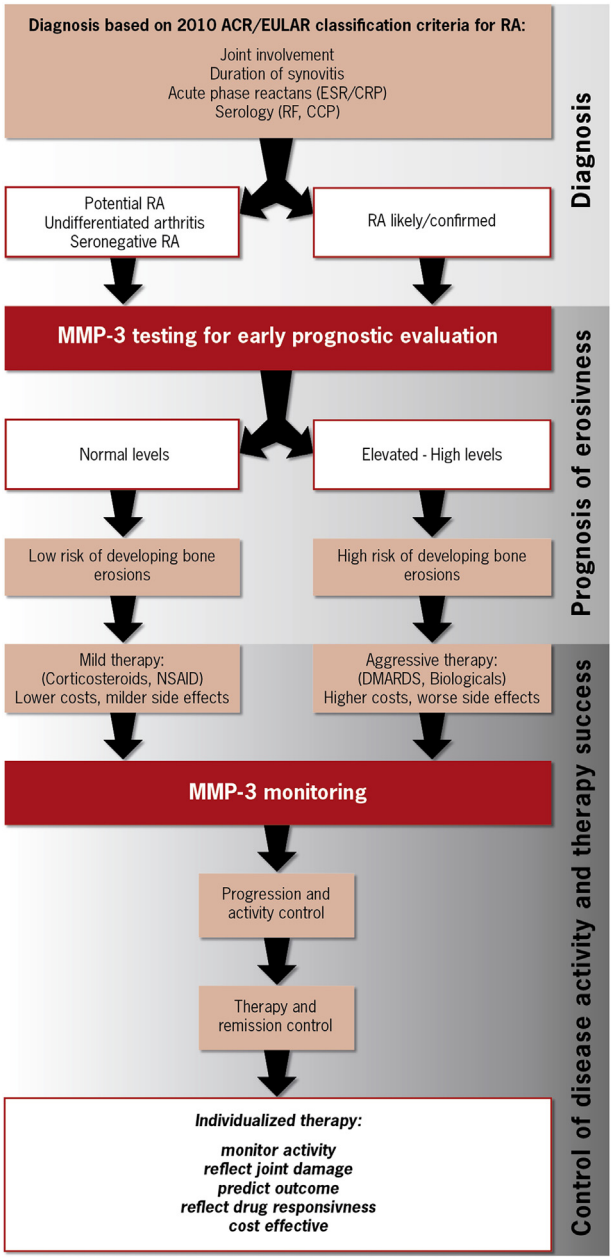

Fig. 2. MMP3-driven flow chart, based on its serum differential levels: normal, elevated, or high titers.

Conclusions

Serum MMP3 titers are useful, reliable, and effective biomarker to monitor and predict RA disease activity, joint and bone damage, radiological abnormalities, disease outcome, and drug responsiveness. It should be embedded in the routine evaluation, monitoring, and treatment of the AR population.

Practice points

- MMP3 correlates positively with disease activity, reflects radiological damage scorings, correlates to joint and bone damage, predicts disease outcome, and is a predictive marker for therapeutic drug responsiveness, in RA patients.
- MMP3 surge, in early stages of RA, goes along the 2010 criteria aimed for early stage diagnosis, early disease modifying antirheumatic initiation, and potential prevention of definitive skeletal and articular damage.
- MMP3 should be introduced as a biomarker in RA workup and during therapy monitoring.

Research agenda

- MMP performances in RA have prompted an urgent need for well-defined guidelines, indicating how and when to use this biomarker.
- Large multicenter placebo-controlled clinical trials are needed to substantiate MMP performances in monitoring RA activity and complication, therapeutic efficiency, and predictability in RA.

Review

No grant support and not funded.

Conflicting interests

MT is the CEO of AESKU.DIAGNOSTICS GmbH& CO.KG.

Submission declaration

This work has not been submitted/published elsewhere.

Provenance and peer review

Commissioned, externally peer-reviewed.

Acknowledgment

The authors would like to thank Mr. Neu Alf for the figure designs, to Ms. Patricia Jeremias and Dr. Ramesh Ajay for editing and reviewing the manuscript.

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