CORRELATION BETWEEN PROGRESSIVE JOINT DAMAGE AND SERUM LEVEL OF MATRIX METALLOPROTEINASES: MMP-3 AND MMP-1 IN EARLY RHEUMATOID ARTHRITIS

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KEY WORDS: PROGRESSIVE JOINT DAMAGE, SERUM MMP-3, MMP-1 IN RA.

ABSTRACT

Background: *There are a group of rheumatoid arthritis (RA) patients for whom traditional markers of outcome are unhelpful. Despite of absence of these markers; still they have progressive damaging arthritis. Expression and activation of matrix metalloproteinases as MMP-3 (stromolysin-1) and MMP-1 (collagenase-1) are increased in RA patients. There are contradictory results of their role as predictors of joint damage.*

Objectives: *To study the role of MMP-3 and MMP-1 as predictors of joint damage in early RA.*

Methodology: *Seventy early RA patients of less than 12 months duration fulfilling the ACR criteria for classification of RA were enrolled in this study. They were 65 females and 5 males with mean age (30.5±3.2) years. Also 30 apparently healthy persons were studied as a control group, 15 males and 15 females with mean age of (33.5 ± 2.8) years. All patients and control volunteers were tested for MMP-3 and MMP-1 basal serum level, using an Enzyme-Linked Immunosorbent Assay (ELISA). The subsequent change of Larsen Radiological Score (Δ Larsen) and Health Assessment Questionnaire (Δ HAQ) were recorded and correlated with MMP-3 and MMP-1 over a 12 months period.*

Results: *The mean basal serum level of MMP-3 and MMP-1 were significantly higher in RA patients than controls ($p<0.05$). MMP-3 and MMP-1 serum levels at presentation of RA patients correlated significantly with basal CRP presentation ($r = 0.40$, $r=0.47$ and $p<0.05$), with ΔLarsen Score ($r = 0.24$, $r = 0.31$ and $p<0.05$), and with ΔHAQ ($r = 0.33$, $r = 0.31$ and $p<0.05$). The group of patients with normal CRP at presentation (≤10mg/dl) showed a significant correlation between MMP-3, MMP-1 and erosive disease during the 12 months duration ($r = 0.62$, $r = 0.47$ respectively and $p<0.05$). The group of patients without erosions at presentation showed that MMP-3 and MMP-1 had stronger correlation with progression in ΔLarsen Score.*

Conclusions: *Serum MMP-3 and MMP-1 of early RA patients correlate significantly with disease activity and may predict functional outcome and radiological joint damage. More prolonged studies with larger numbers of patients are needed to confirm these results.*

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune disease of unknown etiology characterized by chronic synovitis with pannus formation and progressive joint destruction. It is considered by most rheumatologists as locally malignant disease which necessitates early aggressive treatment with disease modifying antirheumatic drugs [(1)]. A number of studies showed that early and aggressive treatment with those drugs (DMARDs) suppresses inflammation and limits joint destruction [(2)].

On the other hand, disease modifying drugs (DMARDs) are potentially toxic and expensive as antitumor necrosis factor-α (TNF-α), which is increasingly used in the disease. It is therefore increasingly relevant to identify which patients will have progressive disease, and a degree of prediction can be achieved using standard measures [(3)]. However there are a group of patients for whom traditional markers of outcome are unhelpful.

This group of patients may have classic picture of RA without traditional bad prognostic feature, but still have progressive joint damaging arthritis. That group and others in that aspect who are non-erosive at presentation and those who do not have an elevated acute phase reactants are especially in need of accurate predictors for prognosis [(4)]. Expression and activation of matrix metalloproteinases (MMPs), such as MMP-3 (stromolysin-1) and MMP-1 (collagenase-1) have been found to be highly enhanced in the synovial fluid of RA patients [(5)]. Early studies failed to find a correlation between serum MMP-3 and MMP-1 levels and the progression of RA i.e. joint damage [(6, 7 and 8)].

On the other hand, recent studies showed positive correlation of these markers in early RA [(9, 10 and 11)]. In our study we discussed this subject with the controversies and assessed the serum MMP-3 and MMP-1 in early RA patients who either had a normal acute phase response or have no joint erosions at presentation.

PATIENTS AND METHODS

Seventy early RA patients were chosen for this study, all of them were diagnosed according to the ACR classification criteria, 1987. They were 65 females and 5 males with mean age (30.5±3.2) years, with age range (27.5y. to 39.5y.). All patients did not have DMARDs before presentations with disease duration less than 12 months. The control group consisted of 30 healthy volunteers without clinical evidence of arthritis; they were 15 females and 15 males with mean age (33.5±2.8).

All patients were subjected to full history and thorough clinical examination including recording of number of swollen joints (SJC), tender joint count (TJC) and visual analogue scale score 10 cm for patient's assessment of disease activity and pain and recording the observer assessment of disease activity (0-4).

Blood samples were taken from the patients for CBC, ESR rheumatoid factor, CRP, ANA and routine blood chemistry, X-rays for hands and feet were taken for all patients (standard P-A view).

Blood samples were taken also from the control group for same analyses.

Detection of MMP-3 and MMP-1:

Enzyme Linked Immunosorbent Assay (ELISA) was used for each of MMP-3 and MMP-1 using commercial kits *(the Binding site, Birmingham, UK).*

Samples were stored at -20^{o}C and the test was made according to the manufacturer's instructions. Radiological data for patient's hands and feet X-ray films were recorded according to Larsen Score at the start of the study and at the end. The changes in Larsen Score (Δ

Larsen) and Health Assessment Questionnaires (ΔHAQ) over 12 months were correlated along with mean of progression in Larsen Score.

Statistics:

To examine the relationship between CRP, ΔHAQ and Δ Larsen Score we used the Peerson correlation coefficient. Linear regression analysis was used to determine the predictability using all the predictable available at base line of study. A further analysis of data was performed on two subgroups separately (i) patients with normal CRP at the start of the study (ii) patients without erosions on the X-rays at the start of the study.

RESULTS

The patients were divided into 2 subgroups A and B:

Subgroup A: Those patients with CRP ≤ 10mg/dl. They were 18 patients, 16 females and 2 males.

Subgroup B: Those patients without erosions, they were 58 patients; they were 55 females and 3 males.

The patients clinical characteristics are shown in table (1). They showed mean disease duration (5.5±2.8) months at the start of the study (range 4.5 to 8.5 months), Fifty five patients had rheumatoid factor positivity (78.6%) and all patients had no DMARDs at the start of our study. The mean rate of progression in Larsen Score over the 12 months was 11.8 for all patients, while it was 9.8 for subgroup B (non-erosive) at the start of the study.

Table (1): Clinical characteristics at the study of the patients with early RA.

Item	Patients (n = 70)	Subgroup A (CRP≤ 10mg/dl) (n = 18)	Subgroup B (non erosive) (n = 58)
Age mean (SD)	30.5 ± 3.5	29.2 ± 2.6	30.1 ± 3.1
Female sex (%)	92.8	88.8	94.8
Disease duration (months)	5.5 ± 2.8	5.2 ± 2.5	5.3 ± 3.2
HAQ mean (range)	12.6 (4-22)	10.2 (6-20)	12.8 (10-23)
CRP (mg/dl) mean (SD)	32.8 ± 3.2	8.2 ± 1.1	36.2 ± 4.1
ESR (mm/h), mean	42.2 ± 4.2	14.2 ± 2.8	41.2 ± 2.4
RF (positivity %)	(78.6)	77.7	84.4
ANA (positivity %)	2.8	1.4	1.4
DMARDs use	0	0	0

The mean serum level of MMP-3 (stromelysin-1) and MMP-1 (collagenase-1) were significantly higher in RA patients than that of the control group. MMP-3 mean serum level was 46.4 ng/ ml in RA patients versus 20.2 ng/ ml in control group ($p<0.001$) and mean serum MMP-1 in RA patients was 44.2 ng/mL versus 12.5ng/ mL for control group ($p<0.001$).

The mean + SD of Larsen Score progression was 13.2 ± 9.8 for total patients and was 11.2 ± 7.8 for non-erosive (group B) at the start of the study and was 22.4 ± 6.51 for erosive patients at start of the study. We divided the patients according to progression of Larsen Score changes into 2 groups (i) group with high Δ Larsen Score (ii) group with low Δ Larsen Score.

Table (2): Correlation coefficients for (Δ Larsen) radiographic damage, function (ΔHAQ) and CRP (basal level).

Item	CRP (basal level)	Δ Larsen	Δ HAQ
MMP-3	0.40	0.24	0.33
MMP-1	0.47	0.31	0.31
CRP (basal)	-	0.30	0.42

p< 0.05 for all values above

We found that patients with a high rate of X-ray progression had a significantly greater level of MMP-1 and MMP-3 at the start of the study (basal level) as compared to those patients with low rate progression (low Δ Larsen). MMP-3 mean value was 52.8 ng/mL versus 40.1 ng/mL (p<0.005).

Table (2) shows that serum MMP-3 and MMP-1 correlated significantly with CRP at the start of the study (basal level), (r = 0.40 and 0.047) respectively. They also correlated significantly with ΔHAQ (r = 0.33 and 0.31) and with Δ Larsen (r = 0.24 and 0.31).

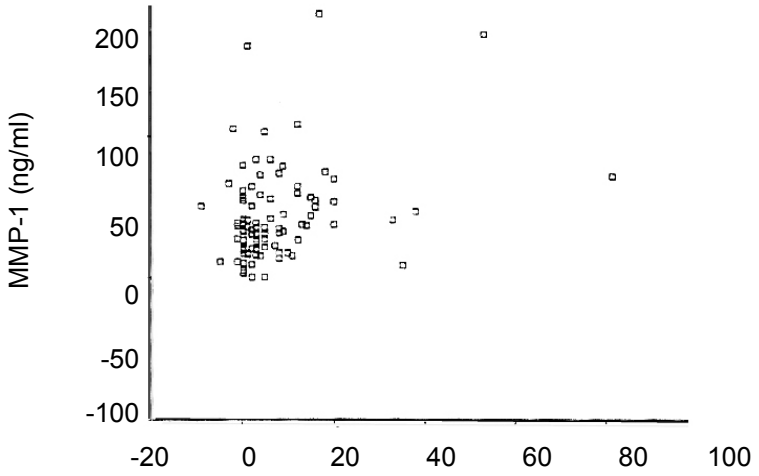

Fig. (1): Scattergraph of baseline serum MMP-1 compared to (Larsen score changes) in over 12 months.

Logistic regression analysis:

A logistic regression was made for all patients to correlate predictors variables at baseline i.e. RF positivity, erosions, non-erosions, sex, ESR, MMP-3, MMP-1 with Δ Larsen Scores during 12 months period.

The result showed that base line erosions with RF positivity and MMP-3 level with RF positivity followed by MMP-1 with RF positivity in order, were the best predictors (r = 0.31, r = 0.42, r = 0.47 and p<0.05) respectively. Logistic regression in patients who were non erosive at presentation (n = 58) showed that the strongest correlation with Larsen Score progression was serum level of MMP-3 at presentation (base line level), (r = 0.341, p< 0.05).

Detailed analysis of patients with normal CRP (CRP ≤ 10 mg/dl):

It showed that there was a significant lower level of MMP-3 and MMP-1 than in patients with high level of CRP (> 10 mg/dl), MMP-3 mean was 36.2 versus 54.3 ng/ml and MMP-1 mean was 30.8ng/ml

versus 53.6 ng/ml, p value <0.001 for all results.

Our results showed that there was a significant correlation between base level of MMP-1 and MMP-3 with presence of erosive disease during the 12 months duration of the study and there was also a significant correlation between base level at presentation of CRP with presence of erosions during the study period of 12 months (r = 0.62 and r = 0.47 respectively and p< 0.05 in all results). On the other hand no significant correlation was found between rheumatoid factor positivity alone and the progressive Larsen Score damage (r = 0.078, p >0.05).

Subanalysis of patients who were non-erosive at presentation:

Fifty eight patients were non-erosive and 12 were erosive at presentation. Logistic regression analysis in this subgroup of patients showed that there was a significant correlation between progressive Larsen Score and serum level of MMP-3 at presentation (r=0.32, p<0.05).

DISCUSSION

One of the standard practices in rheumatology nowadays in the management of RA patients is to introduce the disease modifying anti-rheumatic drugs (DMARDs) early in the disease course, once has diagnosis been established, to prevent joint damage. The majority of DMARDs are either expensive or potentially toxic [(3)]. The old traditional markers of prediction of joint destruction are not helpful for a group of RA patients in whom progressive joint damage goes on despite the absence of these prediction markers [(4)]. Matrix metalloproteinases (MMPs) such as MMP-3 (stromelysin-1) and MMP-1 (collagenase-1) are considerably enhanced in the synovial fluid of RA patients [(5)]. In vitro studies have demonstrated the ability of active MMP-3 to denature all the cartilage components (proteoglycans, fibronectin and collagen IV. Hence they may promote joint destruction in vivo [(12)]. MMP-3 concentrations in synovial fluid of RA patients are several hundred folds higher than in serum but there is a strong correlation between them, and serum MMP-3 is reduced by single intra-articular injection of steroids.

To the contrary, severe sepsis results in markedly elevated level of CRP but not MMP-3 [(13)]. This denotes that MMPs production may be a more specific test for intrasynovial inflammation than CRP. The latter is produced in the liver i.e. distant from the site of inflammation and under the action of many different messenger cytokines. Thus, there is increasing interest in the development of serum markers of activity of MMP-3 which could be helpful in predicting the progression of radiological damage of joints. A few studies have been made in addressing that subject with conflicting results [(6, 7, 8, 9, 10, 11)].

Earlier results failed to show a correlation between MMPs and progression of joint damage in RA. These negative results may be due to either a small number of patients, or a cohort of patients with old established disease. The recent studies however have suggested a role for the use of such markers in early disease [(9, 10, 11)] and that is in concordance with our results. The serum level of MMP-3 in our study was more or less similar to that found by *So et al and Tylor et al.* [(6, 13)], although the variation in other published studies was wide [(14,15)]. The serum level of MMP-1 in these two published studies were 10 ng/ ml and 11.2ng/ ml as compared to 44.2 ng/ml in our study.

Cunnane et al. [(11)] in their study examined RA patients for MMP-1 and MMP-3 and tissue inhibitor of metalloproteinase-1 (TIMP-1) as independent predictors of radiographic

damage and showed a significant correlation between the basal serum level of MMP-1 and the erosion score at presentation and this coincides with our results.

However, they did not find the same correlation with MMP-3 but did correlate with measures of inflammation. They concluded the possibility of uncoupling of the mechanism associated with joint inflammation and joint articualr damage. This is in contrast to our results that found a strong correlation between MMP-1 and MMP-3 basal level and CRP at presentation ($r = 0.40$ and $r = 0.47$ and $p<0.05$). This discrepancy and differences may be due to the difference in the study design. In *Cunnane et al*. study the duration of follow up was 2 years and they used the MMPs levels as serial measures overtime and the main form of analysis was univariate. Our results agree with other previous studies that demonstrated that serum level of MMP-1 and MMP-3 are higher in RA patients than in normal controls [(9, 10 and 11)].

CRP is one of the best available serum predictors of progressive radiological damage nowadays [(16)]. Loss of bone mineral density has been demonstrated to correlate also with patients with elevated CRP level. Suppression to a normal level at least stabilizes this loss [(17)]. Although this is an easy test to perform and is available allover the world, it has draw backs including the fact that CRP is released at sites faraway from the joint (i.e. in the liver) and it is under the effect of a lot of cytokines (mainly interleukin – 1, IL-6 and tumor necrosis factor-α), so it is a non-specific marker of inflammation any-where in the body. Moreover, the predictivity power of the baseline CRP remains less clear [(18)] and some patients noted to have normal CRP and still continue to erode.

The presence of erosive disease at baseline has been associated with poor outcome in our study, but only 17% of our patients were erosive at presentation. Separate analysis was performed in patients who either had a normal CRP or who were non-erosive at presentation to show whether MMPs levels offered any additional benefit [(19)].

In the group of patients who had a normal CRP at presentation, MMP-1 and MMP-3 levels correlated significantly with the presence of erosive disease, as shown in plain X-rays of hands and feet ($r = 0.62$, $r = 0.47$ and $p<0.05$). This is consistent with the current understanding of RA, whereby joints damage begins early usually in the peripheral joints often with normal CRP and then progresses to involve large joints at which point disease mass generates an elevated CRP. It is therefore understandable that markers of local damage as MMP-1 and MMP-3 would be particularly useful at this early stage of disease and before the onset of elevated acute-phase response.

However, it must be noted that the number of patients in this group were small ($n = 18$), so it is not easy to confirm solid conclusions. Rheumatoid factor (IgMRF) was shown to be the only universally accepted marker that consistently predicts progression of joint erosions; specially in patients who are non-erosive at presentation i.e. the group of patients in whom the diagnosis of disease is not sure [(20)].

In our study results, MMP-3 serum level stood out as the strongest predictive marker of progressive radiological joint damage in the linear regression analysis. Furthermore, the predictive value was superior to IgM rheumatoid factor. More studies are needed to confirm the reproducibility of such results at early RA patients, once proven; it is conceivable that RA therapy could be targeted as

preventable rather than just disease modifying.

Conclusions:

Our results showed that MMP-1 and MMP-3 serum levels correlate with disease activity and can predict radiological outcome in early RA. This is more important in patients with a normal CRP and in those patients without early erosions.

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العلاقة بين التدمير المتزايد للمفاصل ومستوي إنزيمات بالدم: م م ب-1 (كولاجينيز-1)، م م ب-3 (ستروموليسين-1) في مرضى الرثيان المفصلي المبكّر

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الهدف من البحث: دراسة دور إنزيمات الدم م م ب-1 ، م م ب-3 كعوامل منبئة لتدمير المفاصل المتزايد في مرض الرثيان المفصلي المبكر.

المرضى وطرق البحث: أجري هذا البحث علي 70 مريضا بالرثيان المفصلي المبكر أقل من 12 شهراً بالإضافة إلي مجموعة من الأصحاء عددهم 30 شخصاً كمجموعة ضابطة. وتم تشخيص هؤلاء المرضي طبقا لمواصفات الجمعية الأمريكية للروماتزم وقد كانوا 65 أنثي و5 ذكور وكان متوسط أعمارهم هو 30.5 عاما وكانت المجموعة الضابطة تتكون من 15 ذكراً و15 أنثي وكان متوسط أعمارهم هو 33.5 عاماً. وقد تم فحص المرضي فحصاً دقيقاً بعد أخذ التاريخ الطبي للمرضي وتم أخذ عينات الدم من المرضي والأصحاء لفحص مستوي إنزيمات الدم م م-1 ، م م-3 قبل البدء في البحث مستخدمين طريقة الإليزا وتم بعد ذلك مقارنة التقدم المتزايد في تدمير المفاصل مقاساً بواسطة "معامل لارسن" واستبيان تقييم الصحة مع مستوي إنزيمات الدم م م ب-1، م م ب-3 لإيجاد العلاقة بينهما علي مدي 12 شهرا هي فترة البحث.

النتائج: أظهرت النتائج أن مستوي إنزيمات الدم م م ب-1، م م ب-3 في مرض الرثيان المفصلي هي أعلي من نظيرتها في الأشخاص الأصحاء وهذا الفرق ذو دلالة إحصائية مفيدة. كما أظهرت النتائج أن هناك ارتباطاً مقيداً إحصائياً بين مستوي إنزيمات الدم م م-1، م م-3 عند بدء البحث ومستوي البروتين المتفاعل – ج "CRR" وكذلك التغير في معامل لارسن لتقييم تدمير المفاصل (دلتا لارسن) والتغير في استبيان تقدير الصحة. بالنسبة لمجموعة المرضي الذين لديهم مستوي البروتين المتفاعل - ج CRR طبيعياً (أقل من 10مجم/ دسيلتر) عند بدء البحث وجدت النتائج أن هناك إرتباطا مفيداً إحصائياً بين مستوي إنزيمات م م ب-1 ، م م ب-3 والتقدم في تدمير المفاصل أما مجموعة المرضي الذين لم تكن مفاصلهم بها أي تدمير فقد أوضحت النتائج أن هناك إرتباطاً مفيداً إحصائياً بين مستوي إنزيمات م م ب-1، م م ب-3 وبين التقدم المتزايد في معامل (لارسن لتقدير تدمير المفاصل).

الاستنتاج: نستنتج من ذلك أن مستوي إنزيمات الدم م م ب-1 ، م م ب-3 ترتبط ارتباطاً إحصائياً مفيداً مع نشاط مرضي الرثيان المفصلي المبكر وأنها قد تستخدم كعامل تنبؤ للتدمير المتزايد في المفاصل.