

SERUM MATRIX METALLOPROTEINASES (MMP-3, MMP-9) AND TISSUE INHIBITOR OF METALLOPROTEINASE-1 (TIMP-1) IN RHEUMATOID ARTHRITIS, PSORIATIC ARTHRITIC AND OSTEOARTHRITIS

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KEY WORDS: *SERUM MMP-3, MMP-9 AND TIMP-1 IN RHEUMATIC DISEASES.*

ABSTRACT

Objective: *To investigate whether serum levels of MMPs and TIMPs are specifically elevated in rheumatoid arthritis as compared to other inflammatory and degenerative joint diseases. We compared serum levels of matrix metalloproteinases (MMP-3, MMP-9) and tissue inhibitor of metalloproteinase (TIMP-1) of RA with psoriatic arthritis (PsA) and osteoarthritis (OA).*

Methodology: *Serum samples were obtained from 30 RA, 20 psoriatic arthritis and 30 knee osteoarthritis patients. Serum concentration of stromelysin-1 (MMP-3), gelatinase B (MMP-9) and TIMP-1 were measured with quantitative sandwich enzyme-linked immunosorbent assay (ELISA) technique. Clinical examination and assessment of disease activity in RA using disease activity score (DAS) were carried out. Radiological evaluation in RA patients using the Larsen scale and in OA patients using the Kellgren and Lawrence scale were also done.*

Results: *Unique serum profiles of MMPs and TIMP-1 were identified in the two inflammatory arthritis groups (RA & PsA). The serum concentrations of MMP-3 and MMP-9 were significantly higher in RA patients than in OA patients used as a control groups ($p < 0.001$). These two MMPs dominated in the*

serum of RA patients than PsA patients ($p < 0.001$). The analysis of the serum concentrations of TIMP-1 was also elevated in RA patients as compared with OA knee patients ($p < 0.001$). Also TIMP-1 was found in a significantly higher concentration in the serum of RA patients than PsA patients ($p < 0.05$). MMP-3 and MMP-9 correlate significantly with disease activity (DAS) in RA patients and with radiological scores.

Conclusion: Serum levels of MMP-3, MMP-9, and TIMP-1 were significantly higher in RA and PsA than OA patients. MMP-3 and MMP-9 could be specific markers of joint inflammation and destruction. These variables are neither specific for RA nor for diseases in which bone erosions occur. These markers were correlated with the clinical activity of the disease. Early detection of these markers may herald progressive course and modulate the lines of treatment.

INTRODUCTION

Matrix metalloproteinases (MMPs) are proteolytic enzymes that can degrade extracellular components (Nagase & Okada, 1997). These enzymes are synthesized as latent pro-enzymes that contain a zinc binding active site, and require Ca^{2+} and proteolytic cleavage for activation. The MMP family includes four different groups of enzymes:

(1) **Collagenases**, which include: (i) interstitial collagenase 1 or MMP-1, (ii) neutrophil-type collagenase 2 or MMP-8 and (iii) collagenase 3 or MMP-13);

(2) **Gelatinases**, which include: (i) gelatinase A or MMP-2 and (ii) gelatinase B or MMP-9;

(3) **Stromelysins**, which include: i) stromalysin-1 or MMP-3, (ii) stromalysin-2 or MMP-10;

(4) **Others** as: matrilysin, stromalysin-3, metalloelastase and membrane-type MMPs that 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 α 2-macroglobulin and tissue inhibitors of matrix metalloproteinases (TIMPs) (Nagase, 1997).

The MMPs play an important role both in normal physiological processes and in pathological conditions such as arthritis. In rheumatoid arthritis (RA) patients, 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*), tumor necrosis factor alpha (*TNF- α*), and growth factors such as epidermal growth factor and platelet-derived growth factor (*Posthumus et al., 1999*).

Matrix metalloproteinases, which are locally produced and activated within the affected joint as a result of cytokine mediated stimulation, could be more specific markers for joint inflammation and especially destruction in rheumatic diseases (*Posthumus et al., 2000*).

MMP-3 is capable of degrading many components of the matrix in the synovial joint including proteoglycans, gelatins, laminin, fibronectin, and collagen III, IV, IX and X. Moreover, MMP-3 is able to activate other MMP such as MMP-1, MMP-7, MMP-8, MMP-9, and MMP-13 (*Posthumus et al., 2000*).

Among the most promising characteristics are circulating levels of proteolytic enzymes: MMPs that degrade cartilage and bone matrix, such as MMP-3, but also MMP-1 are elevated in either sera or synovial fluid of patients with RA. This also accounts for MMP inhibitors such as tissue inhibitor of metalloproteinase 1 (*TIMP-1*).

Elevated levels of serum MMP-3 have been found not only in RA, but also in patients with systemic lupus erythematosus, mixed connective tissue disease, systemic sclerosis, gout, ankylosing spondylitis, calcium pyrophosphate arthritis and psoriatic arthritis. Nevertheless, In RA serum MMP-3 could be a useful variable to evaluate disease activity and outcome (*Posthumus et al., 2000*). It is not clear, however, whether elevated levels of MMP or MMP inhibitors are specific for RA or for erosive joint diseases in general. Accordingly, we compared serum levels of matrix metalloproteinases (*MMP-3, MMP-9*) and tissue inhibitor of metalloproteinase (*TIMP-1*) of RA with other inflammatory (Psoriatic arthritis, (*PsA*) and degenerative joint disease (*osteoarthritis, OA*).

PATIENTS AND METHODS

The material of this study consisted of:

- Thirty rheumatoid arthritis (*RA*) patients diagnosed according to the 1987 American College of Rheumatology criteria (*Arnett et al., 1988*).
- Twenty psoriatic arthritis (*PsA*) patients diagnosed according to the criteria of *Moll and Wright (1973)*.
- Thirty knee osteoarthritis (*OA*) patients diagnosed according to *Altman et al. (1986)* and served as a control group. They were recruited

from the Out-patient Clinic of the Rheumatology & Rehabilitation Department, Ain Shams University Hospitals. They were matched for age and sex.

All patients were subjected to the following:

- Full and detailed medical history paying particular attention to the duration of morning stiffness, joint pain using a visual analogue scale (VAS) from 0 (*no pain*) to 10 (*most severe pain*) (Berry & Huskinsson, 1972), type and number of the affected joints.

- A thorough clinical examination including general and musculoskeletal examination with special emphasis on the number of swollen joints, number of tender joints. The tenderness was graded on a rating scale 0-3 (Ritchie *et al.*, 1968).

- Assessment of disease activity in RA patients according to DAS score using swollen joint count, tender joint count, VAS and ESR (Prevo *et al.*, 1995).

- Plain X-rays for joints of hands, feet and knee joints.

For RA patients, assessment was done according to *Larsen et al.*, (1977); while for OA patients' assessment was done according to *Kellgren & Lawrence* (1957).

Laboratory investigations included:

- 1-Complete blood picture (CBC) using Coulter counter (T660).
- 2-Erythrocyte sedimentation rate (ESR) with Westergren method.
- 3-Rheumatoid factor using Latex fixation technique.

Serum sample preparation:

Blood specimens were clotted for 30 min and then centrifuged for 10 min at 1000 g. Serum aliquots were frozen at - 80° c immediately after sample collection.

Measurement of serum MMPs and TIMP-1:

Serum concentrations of MMP-3, MMP-9 and TIMP-1 were measured with the quantitative sandwich enzyme-linked immunosorbent assay (ELISA) (Biotrak; Amersham Pharmacia Biotech, little, UK) according to the manufacturer's instructions. The sensitivity (*limit of detection*) of the assay system was 2.35 ng/ml for MMP-3, 0.6 for MMP-9 and 1.25 ng/ml for TIMP-1.

Statistical analysis:

Normally distributed clinical data were analyzed with the unpaired student's t-test. The Mann Whitney U-test was employed to analyses differences between non-normally distributed data on MMPs and TIMP-1. Probabilities of differences in frequency distributions were assessed with fisher's exact test. The analysis of correlations between variables was based on Rank Spearman's test®. $p < 0.05$ was considered statistically significant and $p < 0.001$ were highly significant.

RESULTS

Clinical findings:

No significant difference in sex ratio, age or disease duration was observed between patients in the two inflammatory arthritis (PA, PsA) groups as well those with OA. As regard ESR, there was a highly statistical significant difference between patients with inflammatory arthritis (RA, PsA) and OA patients ($p < 0.001$) and a statistically significant difference between RA patients and PsA patients ($p < 0.05$) (Table 1).

Table (1): characteristics of patient groups:

Characteristics	Osteoarthritis (OA)	Psoriatic arthritis (PsA)	Rheumatoid arthritis (RA)	p< & significance		
				OA vs PsA	OAvs RA	RAvsPsA
Females / Males	21/9	15/5	24/6	NS.	NS	NS
Mean age (year)	57.6 ±13.7	52.0 ±12.7	57.7 ± 14.3	NS	NS	NS
Mean disease duration (months)	14.1 ±11.6	17.9 ±7.8	13.4 ± 6.3	NS	NS	NS
ESR (mm/h)	15.4 ±10.8	48.6 ±11.0	62.5 ± 20.1	0.001(HS)	0.001(HS)	0.05 (S)
Morning stiffness (min)	—	144.5 ± 32.9	168.0 ± 43.6	—	—	NS
No. of tender joints	—	13.3 ±2.9	15.1 ± 2.6	—	—	NS
No. of swollen joints	—	13.4 ±2.9	16.9 ± 3.2	—	—	0.01 (HS)
No. of RF +ve patients	—	—	80.0% †	—	—	

RF=rheumatoid factor, NS= not significant

The number of swollen joints was higher in RA patients than PsA patients ($p < 0.01$). No other clinical parameters differed significantly between different groups of arthritis.

All patients were receiving non-steroidal anti-inflammatory drugs (NSAIDs). Sulfasalazine was used in the therapy of five RA patients (16.6%). Seven (35%) PsA patients were being treated with methotrexate as compared with 24 (80.0%) RA patients ($p < 0.01$). Ten (33.3%) RA patients were receiving oral steroids ($p < 0.001$). No patients received local joint steroid injections in the last 3 months before blood samples were taken.

Serum MMP-3 and MMP-9 concentrations:

A two-site ELISA sandwich technique was used to measure the serum concentrations of MMPs. Our main interest was that the levels of MMPs differed between patients with different forms of arthritis.

The serum levels of MMP-3 were elevated in RA patients and PsA patients as compared with OA patients ($p < 0.001$) (Fig 1). MMP-3 was the dominant metalloproteinase in RA patients and clearly differentiated these patients from PsA patients ($p < 0.001$).

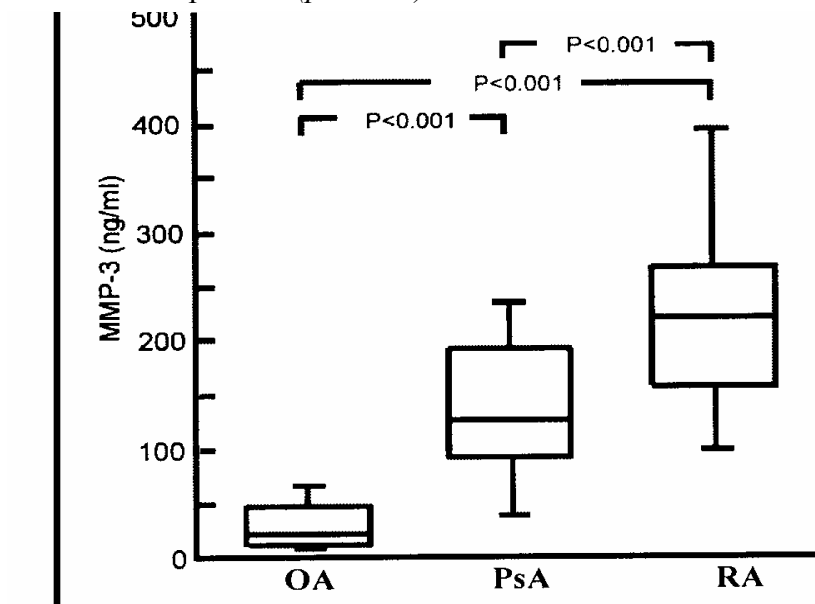


Fig. (1): Serum concentration of stromelysin-1 (MMP-3). The serum levels of MMP-3 were greater in RA and PsA than OA patients. MMP-3 was the dominant MMP in RA and clearly differentiated these patients from PsA patients.

Serum levels of MMP-9 were also increased in RA patients and in PsA patients in comparison with OA patients ($p < 0.001$) (Fig 2). MMP-9 concentration was greater in RA patients than in PsA patients ($p < 0.001$). This metalloproteinase distinguished clearly between the two variants of inflammatory arthritis (RA and PsA).

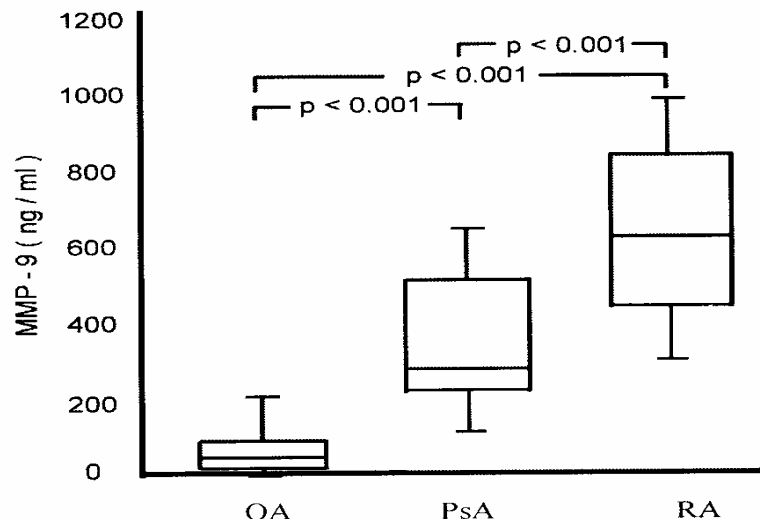


Fig. (2): Serum concentration of gelatinase-B (MMP-9). Serum concentrations of MMP-9 were increased in RA and PsA in comparison with OA patients. The highest serum concentration of MMP-9 correlated with the presence of inflammatory arthritis (PsA & RA).

Serum TIMP-1 concentrations:

Serum concentrations of TIMP-1 were also measured with a two-site ELISA sandwich method. Like the MMPs levels, the serum levels of TIMP-1 were significantly higher in RA patients and PsA patients than OA patients ($p < 0.001$). TIMP-1 reached the highest concentration in RA patients and clearly showed significant difference from PsA patients ($p < 0.05$) (Fig 3).

The analysis of the concentration of matrix metalloproteinases and their inhibitors showed that RA patients, contrary to PsA patients, is associated with relatively high serum concentrations of MMP-3, MMP-9 and TIMP-1. Therefore, serum level of these MMPs and their inhibitors seem to be associated with RA patients, but these are not specific for RA.

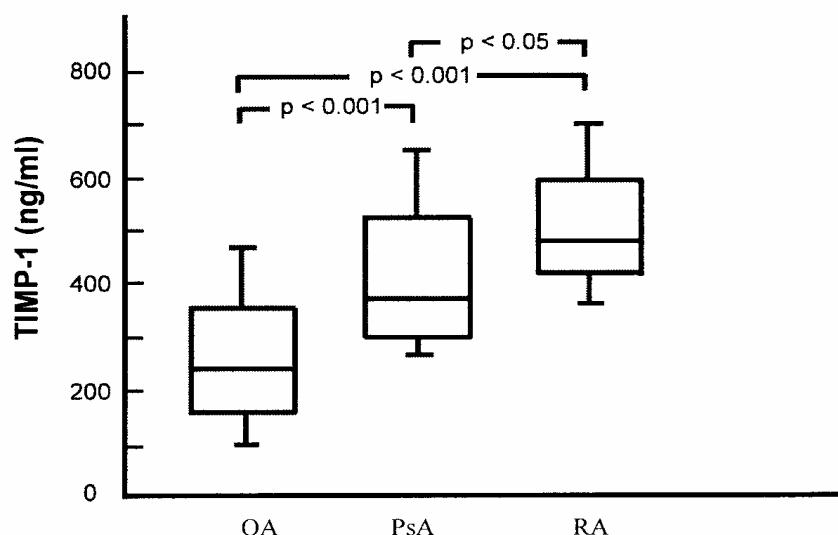


Fig. (3): Serum concentration of TIMP-1. Serum levels of TIMP-1 were elevated in RA and PsA compared with OA patients. The highest concentration of TIMP-1 was in RA patients and the differences in concentration clearly differentiated these patients from PsA patients.

As shown in table (1), about 80% of RA patients were seropositive. No correlations were found between RF and any MMPs or TIMP-1 concentration.

Concentration ratios of MMP-3, MMP-9 to TIMP-1:

As shown in table (3), the concentration ratios of MMP-3, MMP-9 to TIMP-1 were higher in RA patients than in OA patients ($p < 0.001$). They were also higher in PsA than OA patients ($p < 0.001$). However, significant differences between RA patients and PsA patients were observed only for the ratios MMP-9 /TIMP-1 ($p < 0.05$)

Radiological data of the RA patients showed that a large number of patients had a Larsen grade between grade I (10 patients-33.3%) and grade II (11 patients- 36.7 %). While, in OA patients a large number of patients had a Kellgren and Lawrence (K/L) grade between grades 3 (12 patients- 40 %) and grade 4 (8 patients – 26.7 %). In PsA, a large number of patients had joint space narrowing (16 patients -80%).

Correlations between clinical data and serum MMP-3, MMP-9 and TIMP-1 levels:

We found that patients with Larsen score ≥ 4 had higher levels of MMP-3 & MMP-9 than patients with Larsen score ≤ 2 . Also, there was a

positive significant correlation between MMP-3 & MMP-9 and joint space narrowing in RA (*grade II*), OA (*grades 3*) and PsA patients. ($p < 0.05$).

Table (2) shows Correlations between serum concentrations of MMP-3, MMP-9, TIMP-1 and clinical parameters in all 30 RA patients.

Correlation	r	p <	p <
MMP-3			
MMP-9	0.499		0.01
TIMP - 1	0.425		0.01
ESR	0.532		0.001
Morning stiffness	0.542		0.001
Ritchie index	0.458		0.01
No. of swollen joints	0.401		0.05
DAS score	0.631		0.001
MMP-9			
TIMP-1	0.393		0.05
ESR	0.748		0.001
Morning stiffness	0.569		0.001
Ritchie index ;	0.433		0.01
No. of swollen joint	0.561		0.001
Disease duration	- 0.395		0.05
DAS score	0.572		0.001
TIMP-1			
ESR	0.446		0.01
Morning stiffness	0.416		0.05
Ritchie index	0.362		0.05
No. of swollen joints	0.371		0.05

Table (3): Concentration ratios of MMP-3, MMP-9 to TIMP-1.

Ratio	OA	PsA	RA	p <		
				OA vs PsA	RA vs OA	RA vs PsA
MMP-3-TIMP-1	0.137	0.333	0.459	0.001	0.001	NS
MMP-9-TIMP-1	0.263	0.946	1.318	0.001	0.001	0.05 (S)

DISCUSSION

The MMPs play an important role both in normal physiological and pathological conditions such as arthritis. The MMPs play major role in destruction of cartilage and other components of connective tissue in joints. This also accounts for MMPs inhibitors such as TIMP-1 (Ribbens *et al.*, 2000). MMPs are released by synovial fibroblasts, chondrocytes, macrophages, neutrophils and endothelial cells in response to pro-inflammatory cytokines like interleukin-1 (*IL-1*), tumor necrosis factor alpha (TNF- α), and growth factors such as epidermal growth factor and platelet-derived growth factor. They could be more specific markers for joint inflammation and especially joint destruction in rheumatic diseases. (Mauviel 1993).

The clinical assessment of the disease activity of RA is a demanding and often a time consuming task for the rheumatologist. Laboratory variables could be helpful as surrogate markers of RA disease activity. Currently, few laboratory measures are established for monitoring of RA disease activity (Keyszer *et al.*, 1999). C-reactive protein (*CRP*) and erythrocyte sedimentation rate (*ESR*) correlate with the degree of joint inflammation and the development of erosions. However, they are not specific for RA and are commonly elevated in other conditions such as concomitant infections.

In this study, we found that the serum concentrations of MMP-3 and MMP-9 were higher in RA patients than in OA patients ($p < 0.001$). These results are in agreement with Keyszer *et al.* (1999) who found that the levels of MMP-3 and MMP-9 were markedly elevated in RA patients as compared to OA.

Moreover, the elevated levels of MMP-3 and MMP-9 in this study were also seen in psoriatic arthritis as compared to OA patients ($p < 0.001$).

MMP-3 and MMP-9 could be specific markers of joint inflammation and destruction, because they are almost exclusively produced in the inflamed synovium. This was explained by Posthumus *et al.* (1999) who suggested that the serum MMP-3 level is affected by the amount of inflammatory tissue within the joint. Also, Jovanovic (2000) stated that the production of MMP-9 by monocyte/ macrophage is stimulated by TNF-IL-1 and IL-17. These results showed that these variables are neither specific for RA nor for diseases in which bone erosions occur.

There was a statistically significant positive correlation between the levels of MMP-3/ MMP-9 and ESR, morning stiffness, Ritchie index, No. of swollen joints and DAS score. While, there was statistically significant

negative correlation between the level of MMP-9 and Disease duration. This is in accordance with *Ribbens et al. (2000)* who stated that serum MMP-3 levels correlate closely with systemic markers of inflammation and with the disease activity in RA. They also found significant correlations between serum levels of MMP-3 and IL-6 which reflect acute phase response. Also, this is in agreement with *Klimiuk et al. (2002)* who concluded that the serum MMP-3 and MMP-9 profile positively correlated with the clinical activity of the disease.

In our study, we found that there was a significantly higher concentration of TIMP-1 in the serum of RA patients and PsA patients in comparison to OA patients ($p < 0.001$). However, TIMP-1 in the serum of RA patients was higher than in PsA patients and the difference was statistically significant ($p < 0.05$). These results agree with the results of *Yoshihara et al. (1995)*, but not in accordance with *Keyszer et al. (1999)* who reported that levels of TIMP-1 were not significantly elevated in the plasma of RA patients. We postulated that the difference may be due to the differences in the ELISA technique as they investigated plasma samples instead of sera.

TIMP-1 levels showed a significant positive correlation with ESR, morning stiffness, Ritchie index, and No. of swollen joints in RA patients. However, no correlation was found with disease duration or DAS score. These results are in agreement with that of *Keyszer et al. (1998)* who reported significant correlation with ESR, CRP, RF titer.

Overall MMP activity is a balance between the amount of MMP and TIMP-1 present (*Jackson et al., 1998*). In our results the concentration ratios of MMP-3/TIMP-1 and MMP-9/TIMP-1 were higher in PsA than in OA ($p < 0.001$) and higher in RA than in OA ($p < 0.001$). The highest ratios were recorded in RA patients. This indicates that in inflammatory arthritis the low levels of TIMP-1 produced by rheumatoid synovium would shift the balance in favor of increased MMP activity by these cells.

There was a positive significant correlation between MMP-3 & MMP-9 and joint space narrowing in RA (*grade II*), OA (*grades 3*) and PsA patients ($p < 0.05$). This could be explained by *Emery et al. (1995)* who concluded that MMP-3 could be a specific marker of joint inflammation and destruction because it is almost exclusively produced locally, in the inflamed synovium. While *Colnot & Helms (2000)* reported that MMP-9 could digest cartilage proteoglycans and play important roles in chondrocyte apoptosis and osteoclastic bone resorption.

Conclusions:

Our study showed that serum levels of MMP-3, MMP-9, and TIMP-1 were significantly higher in RA and PsA patients than OA patients. Moreover their levels were significantly higher in RA than in PsA. MMP-3 and MMP-9 could be specific markers of joint inflammation and destruction, although these variables are neither specific for RA nor for diseases in which bone erosions occur. These markers correlated with the clinical activity of the disease in RA. Early detection of elevated serum levels of these markers may herald progressive course and may modulate the lines of treatment.

Our data encourage further longitudinal studies to determine the predictive value of MMPs for the development of structural damage in RA.

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انزيم الميتالوبروتينيز البين خلوى الثالث والتاسع والعامل المثبط للعوامل المذيبة للنسيج- في مصل مرضى الرثيان المفصلي والتهاب المفاصل الصدفي والفصال العظمى المفصلي

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هدف البحث: لدراسة مستوى إنزيم الميتالوبروتينيز البينخلوى الثالث والتاسع والعامل المثبط للعوامل المذيبة للنسيج-1 في مصل مرضى الرثيان المفصلي بالمقارنة بمرضى التهاب المفاصل الصدفي ومرضى الفصال العظمى المفصلي.

طريقة البحث: تمت دراسة نسبة مستوى انزيم الميتالوبروتينيز البينخلوى الثالث والتاسع والعامل المثبط للعوامل المذيبة للنسيج-1 بطريقة الاليزا في مصل ثلاثين من مرضى الرثيان المصلي وعشرين من مرضى التهاب المفاصل الصدفي وثلاثين من مرضى الفصال العظمى المفصلي كما تم الفحص الاكلينيكي الشامل مع التركيز على أعراض نشاط المرض والتحليل والأشعات.

نتائج البحث: كان هناك زيادة ذات دلالة إحصائية في مستوى انزيم الميتالوبروتينيز البينخلوى الثالث والتاسع والعامل المثبط للعوامل المذيبة للنسيج-1 في مرضى الرثيان المفصلي ومرضى التهاب المفاصل الصدفي مقارنة بمرضى الفصال العظمى المفصلي. كما كانت هناك علاقة طردية بين هذه الدلالات ومؤشر نشاط المرض (داس) في مرضى الرثيان المفصلي.

كما أظهرت الدراسة عن وجود علاقة طردية بين هذه الدلالات وبين التغيرات المفصلية المشخصة إشعاعيا.

ومما سبق يتضح أن قياس نسبة هذه الدلالات في مصل هؤلاء المرضى يعطى دلالة على شدة إصابة المفاصل وقد يكون له أهمية مستقبلا في اختيار العلاج المناسب لهذه الأمراض ومتابعة تطور ونشاط المرض.