SERUM LEVEL OF MMP-3 IN PATIENTS WITH PSORIATIC ARTHRITIS TREATED WITH TNF-α BLOCKERS

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Abstract: Background: Matrix metalloproteinases (MMPs) are a family of proteolytic enzymes whose primary function is to break down the extracellular matrix. MMPs are important for tissue remodeling and affect cell signaling. MMP-3 (Stromelysin-1, Transin-1) hydrolyzes natural collagen and extracellular matrix components such as proteoglycan, laminin, fibronectin, gelatin and collagen type III, IV and IX and activates the precursor of IL1-beta. Psoriatic arthritis (PsA) is a rapidly developing, debilitating disease, and it is important for patients with it to identify serum biomarkers to predict its development.

Patients and Methods: MMP-3 has been studied in 21 patients with PsA, 16 patients with PsA receiving TNF-α blocker therapy, and 22 patients with gonarthrosis and 15 healthy age-matched adults. All patients were treated and monitored at the University Clinic of Rheumatology, UMHAT “Kaspela“ and UMHAT “Steti Georgi”, Medical University, Plovdiv. The study of MMPs was performed using an ELISA methodology. Statistical processing of the data was performed using the SPSS 23 program with confidence (p<0.001).

Results: The mean MMP-3 value in patients with PsA was 197.00 ± 35.90 pg / ml, in patients with AS 101.08 ± 15.76 ng / ml. The mean MMP-3 in patients with PsA receiving TNF-α blocker therapy and with low clinical disease activity was 50.48 ± 9.22 ng / ml. The mean MMP-3 in patients with gonarthrosis was 42.91 ± 11.72 ng / ml. The mean MMP-3 values in patients with active PsA were significantly different from those treated with TNF-α-blockers and patients with degenerative joint disease and controls (p<0.05).

Conclusion: MMP-3 was significantly increased in patients with PsA compared with patients with osteoarthritis and healthy subjects. Administration of TNF-α blockers gradually leads to a decrease in the serum level of MMP-3 and can serve as a biomarker for disease activity as well as for evaluating the effect of therapy.

Keywords: MMP-3 level, rheumatic diseases, biomarkers

INTRODUCTION
Matrix metalloproteinases (MMPs) are integrated as regulators for tissue homeostasis and immunity in the network of multidirectional communication within tissues and cells (5). The uncontrolled MMP activity can easily become destructive and lead to breakdown of homeostasis (5). The catalytic activity of MMPs is controlled at four different levels: 1) gene expression with transcriptional and post-transcriptional regulation; 2) extracellular localisation and tissue or cell type of MMP release; 3) pro-enzyme activation by removal of the pro-domain; 4) inhibition by specific inhibitors (3, 4, 7). MMP gene expression is primarily regulated at the transcriptional level, post-transcriptional control of mRNA stability by cytokines, nitric oxide or micro-RNA has been recently described as a significant contributing mechanism (3, 4, 5). Secreted MMPs are often associated to the cell membrane, which focuses their activity to specific substrates in the pericellular space (12). Cells use surface receptors, like integrins to inform themselves what protein in the cell periphery has been encountered and consequently, which type of enzyme is needed and where it has to be released (5, 9). MMPs are of outstanding importance in the site-specific cleavage of growth factors and cytokines (3). Through processing of these signalling molecules, MMPs interfere with cellular communication (6). The formation of the skeleton in humans depends on two major ossification processes which require extensive matrix remodelling. While endochondrial ossification is needed for most bones in the body, intramembranous ossification is essential for flat bones (2, 8). MMPs are integrated in the network of multidirectional communication within tissues and cells as important regulators of cell proliferation and differentiation, tissue homeostasis, immune response and several other processes.
Since uncontrolled MMP activity can easily become destructive and lead to breakdown of homeostasis, it has been realised that their activity needs to be tightly regulated at different levels, through epigenetic, transcriptional and post-transcriptional control of gene expression, activation of their pro-enzymes, and inhibition of their activity (5, 8, 9).

Many studies have shown that each level of control implicates several alternative regulatory subunits; some of them are highly specific for single MMPs (5). There is evidence that distinct regulatory patterns of single or small groups of MMPs are associated with and inflammatory diseases, which can be used for selective MMP targeting at the expression level by RNA interference technology or at the protein level by selective inhibitors and blocking antibodies. MMPs are multifunctional proteases with a widespread substrate repertoire (1, 2, 8). The majority of MMP substrates are non-matrix molecules, thus indicating that release of growth factors and cytokines is the predominant function of MMPs (1). Due to their activity, MMPs can be involved in many different signalling networks simply by regulating other proteases, both directly and indirectly through cleavage and inactivation of protease inhibitors (1).

MMP-3 or stromelysin-1 is an enzyme which plays a part in the destruction of cartilage and bone. MMP-3 serum levels are increased in inflammatory rheumatic diseases characterised by joint synovitis, such as RA, polymyalgia rheumatica, psoriatic arthritis, and acute crystal arthritis— that is, whether the diseases are acute or chronic, erosive or not (10). These data strongly suggest that serum MMP-3 reflects synovial inflammation (10). MMP-3 can degrade many components of the extracellular matrix and are correlated with the number of joints affected. Serum MMP-3 has been proposed as a synovial derived marker of inflammation.

To test the hypothesis that MMP-3 is a synovial derived inflammatory parameter, we measured MMP-3 serum levels in patients with psoriatic arthritis, treated with anti TNF-α blockers.

The aim of this study was the investigation of serum level of MMP3 in patients with psoriatic arthritis, treated with anti TNF-α blockers.

### PATIENTS AND METHODS

MMP-3 has been studied in 21 patients with PsA, 16 patients with PsA receiving TNF-α blocker therapy, 14 patients with ankylosing spondylitis (AS), 22 patients with gonarthrosis and 15 healthy age-matched adults. All patients were treated and monitored at the University Clinic of Rheumatology, UMHAT “Kaspela” and UMHAT “Steti Georgi”, Medical University, Plovdiv. The study of MMPs was performed using an ELISA methodology, using a one step sandwich method. The range of the assay was 22.58 ± 2.95 ng / ml.

Serum levels of MMP-3 did not follow a Gaussian distribution and results are expressed as median values with the 25–75 centiles. Between-group differences were analysed with the non-parametric Mann-Whitney U test. p Values were further corrected for multiple testing. The Wilcoxon rank sum test was used to compare paired populations. Statistical processing of the data was performed using the SPSS 23 program with confidence (p <0.001).

### RESULTS

The mean MMP-3 value in patients with PsA was 197.00 ± 35.90 pg / ml, in patients with AS 101.08 ± ng / ml. The mean MMP-3 in patients with PsA receiving TNF-α blocker therapy and with low clinical disease activity was 50.48 ± 9.22 ng / ml. The mean MMP-3 in patients with gonarthrosis was 42.91 ± 11.72 ng / ml (Tabl.1)

### Tabl.1. Serum level of MMP3 values in patients with PsA, AS, gonarthrosis in control subjects (x±Sx) pg / ml.

<table>
<thead>
<tr>
<th>Patients(N)</th>
<th>$\bar{x}$</th>
<th>SD</th>
<th>t1</th>
<th>t2</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>PsA</td>
<td>21</td>
<td>197.00</td>
<td>35.90</td>
<td>4.87</td>
<td>3.36</td>
</tr>
<tr>
<td>AS</td>
<td>14</td>
<td>101.08</td>
<td>15.76</td>
<td>4.89</td>
<td>2.96</td>
</tr>
<tr>
<td>PsA and anti-TNF-a treatment</td>
<td>16</td>
<td>50.48</td>
<td>9.22</td>
<td>2.88</td>
<td>0.50</td>
</tr>
<tr>
<td>Gonarthrosis</td>
<td>22</td>
<td>42.91</td>
<td>11.72</td>
<td>1.68</td>
<td>-</td>
</tr>
<tr>
<td>Controls</td>
<td>15</td>
<td>22.58</td>
<td>2.95</td>
<td>1.68</td>
<td>-</td>
</tr>
</tbody>
</table>

T1 – difference to controls

T2 - difference to patients with gonarthrosis
The mean MMP-3 values in patients with active PsA were significantly different from those treated with TNF-α-blockers and patients with degenerative joint disease and controls (p <0.05).

**DISCUSSION AND CONCLUSION**

These data coincide with those of Löffek et al (5) and Aiken et al (1), who found that there was a significant increase in serum level of MMP3 in inflammatory joint disease, but contradicted the results of the same authors, who find that in patients with activated arthropathy MMP3 was elevated. In conclusion, our results show that MMP-3 serum levels are increased in inflammatory rheumatic diseases characterised by joint synovitis. They are normal in non-inflammatory rheumatic diseases and in inflammatory diseases without synovitis, but are significantly increased in patients treated with TNF-α-blockers. Our data therefore strongly suggest that the serum determination of MMP-3 levels is an easy method for quantifying synovial inflammation and should complete the biological assessment of synovial inflammatory diseases. MMP-3 was significantly increased in patients with PsA compared with patients with osteoarthritis and healthy subjects. Administration of TNF-α blockers gradually leads to a decrease in the serum level of MMP-3 and can serve as a biomarker for disease activity as well as for evaluating the effect of therapy.

MMP-3 can be used as a safe biomarker for active psoriatic arthritis, unlike its value for activating arthropathy. Because of these differences in results, we do not recommend MMP3 alone to evaluate the activity of rheumatologic diseases, MMP3 should be used as part of a general algorithm for disease assessment, along with other biochemical and instrumental data

**LITERATURE**


