Serum MMP-1 and TIMP-1 levels are increased in patients with psoriatic arthritis and their siblings

A. Myers, R. Lakey, T. E. Cawston, L. J. Kay and D. J. Walker

Objective. To determine matrix metalloproteinase-1 (MMP-1) and tissue-inhibitor metalloproteinase-1 (TIMP-1) serum levels in patients with psoriatic arthritis (PsA) and to compare this with their siblings and local blood donor controls. PsA is an interesting condition in which to study metalloproteinases because there are variations in the level of destructiveness, including a significant proportion of cases without destructive change. This is unlike rheumatoid arthritis (RA) which is more uniformly destructive and where MMP-1/TIMP-1 levels are known to be elevated.

Methods. MMP-1 and TIMP-1 serum levels were determined by enzyme-linked immunosorbent assay (ELISA) in (a) index cases with PsA (subtype: RA n = 43, distal interphalangeal disease n = 2, oligoarthritis n = 15, spondyloarthropathy n = 9, enthesitis n = 1), (b) siblings with PsA, (c) siblings with psoriasis (Ps), (d) unaffected siblings and (e) local controls. Patients with Ps were divided according to the onset of disease: type I disease, onset before age 40 yr and type II, onset after age 40 yr.

Results. MMP-1 and TIMP-1 levels were significantly increased in both the index cases and the group including all siblings compared with the controls (P < 0.0001). There was no statistical difference in MMP-1 or TIMP-1 levels between index cases and their siblings. There was no difference in serum MMP-1 level between the different subtypes (Moll and Wright) of PsA, but there was an increased level of serum TIMP-1 in patients with rheumatoid pattern (P = 0.05). In the index cases there were increased levels of TIMP-1 in type II onset psoriasis (P = 0.03) but no difference in MMP-1 levels.

Conclusion. MMP-1 and TIMP-1 serum levels are elevated in PsA. This is greatest in RA pattern PsA. These levels were also elevated in unaffected siblings suggesting that genetic factors may be important. TIMP-1 levels were elevated in psoriasis alone, more so in late onset psoriasis, suggesting that the pathological processes of early and late onset psoriasis may be different.

Key words: Psoriatic arthritis, Matrix metalloproteinases, Tissue inhibitor metalloproteinases, Psoriasis.
In psoriasis it has been shown that the majority of epidermal T lymphocytes found in psoriatic lesions produce interferon-γ and no or very little IL-4, indicating that these cells belong to the TH1 subset [25]. Moreover, these cells produce high amounts of IL-2 but little or no IL-10 or tumour necrosis factor-α.

IL-2 is an inflammatory cytokine that is also found in RA. The amount of IL-2 present in the synovial fluid of patients with RA is low compared with other cytokines. It is present in nearly all RA fluids but absent from fluids from patients with osteoarthritis [26]. Anti-cytokine therapy for RA targets inflammatory cytokines, such as TNF-α and IL-1. Unfortunately, when treatment ceases, disease activity can increase once again. A recent placebo-controlled trial in RA of an anti-IL-2 agent (DAB486 IL-2) has revealed a modest improvement in disease activity [27].

We have measured serum MMP-1 and TIMP-1 levels in patients with PsA and compared this with sibling and local controls. Serum levels in sibling controls will enable us to determine whether these enzymes are associated with PsA or whether they are genetically determined.

Patients and methods

Patients

The Freeman Hospital rheumatology database was searched for prevalent cases of PsA (irrespective of rheumatoid factor status). All available and consenting patients, and consenting siblings within a 50-mile (80 km) radius of Newcastle upon Tyne were assessed. Clinical documentation included extent of psoriasis (skin, nail and scalp involvement), presence of enthesitis and pattern of joint involvement.

Serum samples were collected from (a) index cases with PsA (subtype: RA n = 43, distal interphalangeal disease (DIP) n = 2, oligoarticular n = 15, spondyloarthropathy n = 9, enthesitis n = 1), (b) siblings with PsA (n = 15), (c) siblings with psoriasis (Ps) (n = 21), (d) unaffected siblings (n = 67) and (e) local healthy blood donor controls (n = 98). Table 1 illustrates the demographics of the subjects included in the study.

In patients with PsA the pattern of disease was classified according to Moll and Wright’s classification [28] and enthesitis was included as a separate subset. Patients with psoriasis were divided according to the onset of disease: type I disease, onset before age 40 yr, and type II, onset after age 40 yr [29].

Laboratory analysis

Total MMP-1 assay. The enzyme-linked immunosorbent assay (ELISA) measures both proenzyme and active enzyme. The limit of detection of this assay was 5 ng/ml. The technique used has been slightly modified from that previously published [11]. Plates were coated with 2 ng/ml RRU-81L antibody and samples diluted in protein diluent (phosphate-buffered saline containing 9.1% Tween and 0.5 mg/ml bovine serum albumin). All other conditions and times were identical to the original protocols.

Total TIMP-1 assay. The ELISA used measures free and bound TIMP-1, and was performed using a method previously reported [30].

Table 1. Characteristics of patients included in the study groups

<table>
<thead>
<tr>
<th>Case Type</th>
<th>n</th>
<th>Mean age ± s.d. (yr)</th>
<th>% Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Index cases (PsA)</td>
<td>70</td>
<td>49.3 ± 10.9</td>
<td>54.3</td>
</tr>
<tr>
<td>Siblings (PsA)</td>
<td>15</td>
<td>48.9 ± 12.6</td>
<td>93</td>
</tr>
<tr>
<td>Siblings (Ps only)</td>
<td>15</td>
<td>46.9 ± 13.9</td>
<td>73</td>
</tr>
<tr>
<td>Unaffected siblings</td>
<td>67</td>
<td>49.6 ± 14.7</td>
<td>64.2</td>
</tr>
<tr>
<td>Local controls</td>
<td>98</td>
<td>34.2 ± 11.0</td>
<td>39.8</td>
</tr>
</tbody>
</table>

Statistical analysis

Data were analysed using the statistical software package Arcus Biostat version 1.1 in conjunction with Microsoft Excel. Because the patients’ serum levels of MMP-1 and TIMP-1 did not follow a Gaussian distribution, results are given as median values with the interquartile range. Differences between median scores were analysed with the non-parametric Mann–Whitney U-test and for comparisons between different study groups we used the Kruskal–Wallis one-way analysis of variance.

Ethical approval was obtained from Newcastle and North Tyneside Joint Ethics Committee.

Results

Serum levels of MMP-1 and TIMP-1 assayed in the healthy controls were normally distributed.

We compared the serum levels of MMP-1 and TIMP-1 in our PsA and sibling populations with local control data (Figs 1 and 2). MMP-1 and TIMP-1 levels were significantly increased in both the index cases and the group including all siblings (irrespective of presence of psoriasis) compared with the controls (P < 0.0001). Using the Mann–Whitney test there was no statistical difference between the index cases (all of whom had PsA) and the siblings, or between siblings with or without psoriasis. There was no difference in levels of either MMP-1 or TIMP-1 between male and female patients. Also there was no correlation with the markers of inflammation, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP).

MMP-1 and TIMP-1 levels were analysed according to the pattern of joint involvement, using Moll and Wright’s classification. The only difference found between the groups was an increased level of TIMP-1 in patients with RA pattern (median 852 ng/ml, range 534–3969; P = 0.05) when compared with other disease subtypes (data not shown). It has been suggested by Veale et al. [31] that a simpler classification comprising three subgroups (asymmetrical oligoarthritis, symmetrical polyarthitis, predominant spondylitis) may be more clinically relevant. Using Veale’s classification we confirmed our initial findings that there was no difference in serum MMP-1 levels between the subgroups and there was an increased level of TIMP-1 in patients with a symmetrical polyarthritis (median 851 ng/ml, range 534–3936; P = 0.03).

When our data were analysed according to the age of onset of psoriasis in index cases (type I onset < 40 yr, type II onset > 40 yr), we found no difference in MMP-1 levels but a significant increase in TIMP-1 levels in type II disease (n = 15, P = 0.03) (Fig. 3) compared with type I disease (n = 56). A plot of patients’ ages vs MMP-1 or TIMP-1 showed no correlation. There was no difference in either MMP-1 or TIMP-1 levels and type of psoriasis in the sibling cohort.

Discussion

This is the first study assessing serum MMP-1 and TIMP-1 levels in psoriatic arthritis. Our results show that serum MMP-1 and TIMP-1 levels are increased in PsA patients compared with controls (P < 0.0001). Moreover, increased MMP-1 and TIMP-1 levels were also found in the siblings irrespective of concomitant inflammatory arthritis or psoriasis. This may suggest that metalloproteinase levels are genetically determined or may predict future disease, either PsA or psoriasis, in unaffected siblings.

There was a trend for those patients with rheumatoid pattern PsA or a DIP pattern of joint involvement to have increased MMP-1 levels, but this did not achieve statistical significance. A larger study is required to confirm or refute this observation. We were unable to demonstrate differences between the remaining subtypes of PsA. However, there was a significantly increased level...
of serum TIMP-1 in patients with rheumatoid pattern disease ($P = 0.05$). These findings were consistent irrespective of the disease classification used [28, 31]. TIMP-1 levels in patients with RA are known to correlate with disease activity (CRP and ESR) [19, 32], therefore this increased serum level in patients with rheumatoid pattern PsA may be a reflection of the number of joints affected (by definition, patients with rheumatoid pattern PsA have more joints involved, therefore more chance of active synovitis than other PsA subtypes).

Our data reveal significantly increased levels of MMP-1 and TIMP-1 in siblings with psoriasis alone compared with controls ($P < 0.0001$). There was no difference in metalloproteinase levels between the patterns of skin involvement of psoriasis in index cases or siblings, however there was a significant increase in TIMP-1 levels in type II onset psoriasis (onset age > 40 yr). We have shown that, as in patients with RA [13, 19], MMP-1 and TIMP-1 levels in patients with PsA do not correlate with age, therefore this observation that TIMP-1 levels are increased in type II onset...
psoriasis suggests a link with cutaneous psoriasis and warrants further investigation. If psoriatic lesions are known to be inflammatory and plaque cells are producing cytokines, then it is possible that metalloproteinases are induced and therefore also playing a role in the pathogenesis of psoriasis.

In conclusion, our results show increased levels of MMP-1 and TIMP-1 in index cases with PsA and in their siblings compared with controls. We also found increased levels of TIMP-1 in subjects with rheumatoid pattern PsA, but this needs validating in a larger study. Finally, we also demonstrated increased levels of TIMP-1 in type II onset psoriasis. Metalloproteinases are known to play an important role in the pathogenesis of rheumatoid arthritis; this study has suggested that there is a difference between the disease subtypes of psoriatic arthritis and types of psoriasis, which warrants further work.

The authors have declared no conflicts of interest.

References
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