Matrix Metalloproteinases as Novel Disease Markers in Takayasu Arteritis

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Background—Takayasu arteritis (TA) is a chronic vasculitis that primarily affects large elastic arteries. Monitoring of disease activity is crucial because the disease tends to progress despite treatment with glucocorticoid and/or immunosuppressive agents. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) have generally been used as disease activity markers, but these are nonspecific inflammatory markers and lack the sensitivity and specificity to accurately monitor the disease status. Given the histological findings characterized by destruction of elastic fibers, we hypothesized that matrix metalloproteinases (MMPs) could be useful as markers of disease activity in TA.

Methods and Results—A consecutive series of 25 patients with TA were enrolled in this study. According to the National Institutes of Health criteria of disease activity, 11 were in an active phase and the remaining 14 were in remission. Circulating levels of MMP-2, MMP-3, and MMP-9 were determined by ELISA in all patients with TA and controls. MMP-2 levels were higher in patients with TA than in controls, but no correlation was found between serum MMP-2 and disease activity score. In contrast, MMP-3 and MMP-9 levels in patients with active disease were higher than in patients in remission and controls, and a positive correlation was demonstrated between circulating levels of MMP-3 or MMP-9 and disease activity score. The high levels of MMP-3 and MMP-9 improved when patients underwent remission.

Conclusions—The present results indicate that MMP-2 can be helpful in diagnosing TA and that MMP-3 and MMP-9 can be used as activity markers for TA. (Circulation. 2003;108:1469-1473.)

Key Words: aorta ■ arteries ■ diagnosis ■ metalloproteinases

Takayasu arteritis (TA) is an idiopathic vasculitis that affects primarily large elastic arteries such as the aorta and its major branches, and women of reproductive age are most often affected.1,2 The disease tends to progress despite treatment with glucocorticoid and/or immunosuppressive agents. Therefore, once the diagnosis of TA is made, it is essential to determine the degree of disease to choose the appropriate therapeutic strategy. To estimate disease status, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) have generally been used as disease activity markers. However, these markers have been reported to lack sensitivity and specificity for accurately monitoring disease status.3–5 It is therefore crucial to identify more sensitive and conventional markers of underlying disease activity so that patients can avoid receiving unnecessarily high doses of glucocorticoids and/or immunosuppressive agents.

In TA, the earliest change appears to be a granulomatous inflammation in the adventitia and outer layers of the affected arteries, followed by gradual progression to a panarteritis with inflammatory mononuclear cell infiltration.2 The normal architecture of the vessel is disrupted, resulting from histologically characterized degeneration of the elastic lamella in the media of affected elastic arteries.3–5 The process eventually produces intimal thickening and scarring, and aneurysms form in the weakened arterial walls, particularly when the aorta itself is involved. In this process, proteases secreted from infiltrated cells are thought to play some role in the destruction of elastic fibers.

Elastin is the major component of elastic fibers, synthesized by smooth muscle cells and critical to the integrity of many tissues. There are only a few enzymes that can degrade elastin. Among the types of elastolytic proteinases, matrix metalloproteinases (MMPs) can be induced in response to cytokines implicated in a variety of inflammatory processes.6 We hypothesize this induction of MMPs in inflammatory diseases may be involved in the formation of vascular lesions in these diseases. In fact, increased levels of MMPs have been reported recently in other vasculitides. Sorbi et al7 reported that both circulating MMP-9 mass and activity are elevated in giant cell arteritis. Senzaki et al8 reported that patients with Kawasaki disease and coronary arterial lesions had higher plasma MMP-9 levels than febrile disease controls, and those...
levels were reduced after γ-globulin therapy. These reports suggest that increased tissue levels of MMPs were involved in the occurrence and development of vascular lesions. However, the relation of circulating MMPs to TA has yet to be elucidated.

In the present study, we focused on MMPs, which degrade elastin and collagens, and measured serum MMP-2 and MMP-3 levels and MMP-9 concentrations in 25 TA patients. We show that circulating levels of MMPs may be helpful in diagnosing TA and useful as activity markers for TA.

### Methods

### Subjects

We investigated a consecutive series of 25 patients with TA (1 male and 24 females, aged 20 to 67 years) referred to the Department of Internal Medicine and Molecular Science, Osaka University Hospital from October 1997 to September 2002. The diagnosis of TA was based on the presence of symptoms and signs of ischemic, inflammatory large-vessel disease, as well as supportive arteriographic findings. All patients fulfilled more than 3 of the 1990 American College of Rheumatology criteria for classification of TA. None of them had cranial symptoms, a clinical picture of temporal arteritis, or polymyalgia rheumatica. All patients were evaluated by National Institutes of Health (NIH) criteria for disease activity: (1) presence of systemic features such as fever or musculoskeletal problems (no other cause identified); (2) elevated ESR; (3) presence of features of vascular ischemia or inflammation, such as claudication, diminished or absent pulse, bruit, vascular pain (carotodynia), or asymmetrical blood pressure in either upper or lower limbs (or both); and (4) typical angiographic features.

A complete angiogram was performed if active disease was suspected. In the other patients, the absence of new vascular lesions was confirmed by either angiography or ultrasonography. New onset or worsening of each of the above-mentioned features signifies absent; 1, present.

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*F indicates female; M, male; A, angiography; MMF, mycophenolate mofetil; MRA, MR angiography; AZT, azathioprine; US, ultrasound; and MTX, methotrexate. Zero signifies absent; 1, present.

†Presence of features of vascular ischemia or inflammation such as claudication, diminished or absent pulse, bruit, vascular pain (carotodynia), or asymmetrical blood pressure in either upper or lower limbs (or both).

‡Fever or musculoskeletal problems (no other cause identified).
Serum and Plasma Samples
Venous blood was collected into sterile tubes, and the sera and plasma were frozen and stored at −80°C until the assays were performed.

MMP-2, MMP-3, MMP-9, and Tissue Inhibitor of Metalloproteinases Type 1 Assays
Serum levels of MMP-2, MMP-3, and tissue inhibitor of metalloproteinase-1 (TIMP-1) and plasma levels of MMP-9 were measured in 25 patients with TA by use of ELISA systems (Daiichi Fine Chemical Co, Ltd). Circulating levels of MMP-9 were measured in plasma instead of serum because the MMP-9 levels were irregularly elevated during the serum separation. This phenomenon was probably due to the release of MMP-9 from the platelets during the coagulation process, according to the manufacturer’s data. A group of healthy subjects matched for age and gender (n=20, aged 24 to 45 years) were also studied as a control.

Statistical Analysis
Data were expressed as mean±SD. Differences between groups were analyzed by the Mann-Whitney U test with StatView 5.0 software. A Spearman correlation coefficient was determined to evaluate the correlation between circulating levels of MMP-2, MMP-3, or MMP-9 and disease activity score. A value of P<0.05 was considered statistically significant.

Results
We examined the correlation between disease activity and levels of MMP-2, MMP-3, and MMP-9. Figure 1 and the Table show the serum MMP-2 and MMP-3 and plasma MMP-9 levels of 25 patients with TA and healthy control subjects. Mean [SD] serum levels of MMP-2 (955 ng/mL [194]) and MMP-3 (151.8 ng/mL [42.9]) and plasma level of MMP-9 (119.7 ng/mL [77.5]) were all significantly higher in patients with active disease than in controls (670 [82], 39.7 [19.9], and 27.7 ng/mL [11.2], respectively; P<0.0001, P<0.0001, and P<0.0001, respectively). Although serum MMP-3 (48.1 ng/mL [24.0]) and plasma MMP-9 (41.8 ng/mL [24.9]) levels in patients in remission were not significantly different from controls, serum MMP-2 (1009 ng/mL [198]) levels were elevated irrespective of disease activity. There was no significant difference in serum MMP-2 levels between patients in the active phase and those in remission.

To confirm the correlation of serum MMP-2 and MMP-3 or plasma MMP-9 concentrations with disease activity in patients with TA, we calculated Spearman correlation coefficients between either MMP-2, MMP-3, or MMP-9 concentration and disease activity score (Figure 2). No correlation was found between serum MMP-2 and disease activity score (r=−0.164, P=0.4216). In contrast, a positive correlation was found between both serum MMP-3 and plasma MMP-9 level and disease activity score (MMP-3: r=0.750, P<0.001; MMP-9: r=0.675, P<0.001).

Of 11 patients with active TA, 6 underwent remission and were evaluated for circulating levels of MMPs in remission (Figure 3). There was no significant change in serum MMP-2 levels between the active phase and remission. In contrast, in all patients, an improvement of clinical signs and symptoms was associated with a marked reduction in circulating MMP-3 and MMP-9 levels (P<0.05 versus active, Wilcoxon signed-rank test) compared with values recorded during the active phase.

Finally, serum levels of TIMP-1, an inhibitor of MMPs, were measured in all TA patients. As shown in the Table, serum TIMP-1 levels were significantly lower in TA patients (152.1 ng/mL [57.3], P<0.05) than in controls (177.0 ng/mL [32.6]). There was no significant difference (P=0.1626) in serum TIMP-1 levels between patients in an active phase (159.7 ng/mL [44.4]) and those in remission (146.1 ng/mL [66.7]).

Discussion
It has been reported that the unplanned tapering off of glucocorticoid therapy was associated with disease relapse in more than 40% of patients.3 The most commonly used NIH criteria for active disease have been accepted as reliable criteria for active disease have been accepted as reliable.
measures of disease activity\textsuperscript{4,5} but require an angiographic examination for scoring. The invasiveness and cumulative radiation toxicity of this procedure limit its use in monitoring disease progression. ESR and CRP have been used as conventional inflammatory markers; however, they lack sensitivity and specificity.\textsuperscript{3,4} In a prospective report of 60 patients the NIH study, Kerr and colleagues\textsuperscript{4} observed that 72% of patients with TA had elevated ESR, and only in 56% of patients did ESR return to normal, even when the disease was in clinical remission according to the NIH criteria of disease activity. In our observation, all patients with active disease showed elevated levels of ESR and CRP, but ESR and CRP levels remained higher in 29% and 39% of patients in clinical remission, respectively. Tissue factor, von Willebrand factor, thrombomodulin, tissue plasminogen activator, intercellular adhesion molecule-1, vascular cell adhesion molecule-1, E-selectin, and platelet and endothelial cell adhesion molecule-1 have all been investigated for their usefulness as disease markers, but none could distinguish between patients with active TA and healthy volunteers.\textsuperscript{10} These results highlighted the difficulties of using nonspecific inflammatory markers in this condition. It is therefore crucial to identify conventional diagnostic and disease activity markers that can provide an adequate evaluation of treatment efficacy and guide therapeutic decision making for individual patients with TA.

MMPs comprise a family of calcium-dependent zinc endoproteinases and might pathologically participate in a variety of inflammatory responses.\textsuperscript{9} MMP-2, also known as 72-kDa gelatinase, which can digest gelatin, type IV collagen, and elastin, is constitutively expressed in mesenchymal cells such as fibroblasts and smooth muscle cells.\textsuperscript{11} We demonstrated that MMP-2 levels were higher in patients with TA than in healthy controls, regardless of disease activity, and that a high concentration of MMP-2 was helpful in diagnosing TA. MMP-3, also known as stromelysin A, is secreted mainly by fibroblasts and smooth muscle cells.\textsuperscript{12} MMP-9, or 90-kDa gelatinase, is produced by mononuclear cells, including neutrophils, macrophages, and T lymphocytes.\textsuperscript{13} Cytokines, including interleukin-6 and RANTES, which can accelerate the production of MMP-3 by mesenchymal cells\textsuperscript{14} and of MMP-9 by inflammatory cells,\textsuperscript{15} are secreted in inflammatory conditions and are reported to increase in patients with active-phase TA.\textsuperscript{16} Thus, we speculate that increased levels of cytokines within the lesions induce production of MMP-3 and MMP-9 from infiltrated mononuclear cells and/or smooth muscle cells, which results in the destruction of elastic fibers in the arterial media. In the present study, circulating levels of MMP-3 and MMP-9 in patients with active disease were higher than those in patients in remission or controls. A positive correlation was observed between both MMP-3 and MMP-9 levels and disease activity score, and the elevated levels of MMP-3 and MMP-9 improved when patients entered remission. Mean [SD] MMP-3 levels (95.9 ng/mL [38.3]) were still significantly higher than those of controls (39.7 ng/mL [9.9]) and patients in remission (48.1 ng/mL [24.0]) when they were measured soon after the patients underwent remission. However, those MMP-3 levels became lower (54.1 ng/mL [16.1]), comparable to those of patients in remission and controls, 3 months later (data not shown), which suggests the existence of a time lag between clinical remission and normalization of MMP-3 levels. In addition, serum levels of TIMP-1 were lower in TA patients than those in controls. The results suggest that the elastolytic activity in TA patients was exacerbated by the imbalance between MMPs and TIMPs. Yoshihara et al\textsuperscript{17} reported that the imbalance of the amount of MMPs and TIMPs might be a determinant of whether MMPs attack the cartilage extracellular matrix in rheumatoid arthritis. An inadequate counterexpression of TIMP-1 and imbalance of MMPs/TIMPs might represent a crucial event for the development and perpetuation of tissue damage. The finding reinforced our concept that exacerbated elastolytic activity is involved in the destruction of elastic fibers in TA. Thus, the present findings suggest that MMPs play a role in the pathophysiology of TA and could reflect disease activity.

The cutoff values that gave the highest sensitivity and specificity were 800 and 100 ng/mL for MMP-2 and MMP-3, respectively. With these values, the sensitivity and specificity were 96% and 100%, respectively, for MMP-2 as a diagnostic marker and 91% and 100%, respectively, for MMP-3 as a disease activity marker. As to MMP-9 as an activity marker, cutoff values of 90 and 75 ng/mL gave sensitivity and specificity of 45.5% and 100%, respectively, and 63.6% and 81.8%, respectively. In this respect, MMP-3 is a more suitable marker for disease activity than MMP-9, but we think that the combination of MMP-3 and MMP-9 may allow us to estimate more accurate disease activity. Patient 18 was the only patient who had a false-negative result for MMP-2 as a diagnostic marker when the above cutoff value was applied. Interestingly, only this patient took methotrexate in addition to corticosteroids. It might be that methotrexate administration suppressed serum MMP-2 levels in this patient. A similar effect on serum MMP-3 levels by methotrexate therapy during the course of treatment in patients with rheumatoid arthritis has been reported.\textsuperscript{18} Patient 10 had low levels of
serum MMP-3, although she was in an active phase. It is of interest that this patient also had low levels of TIMP-1, which resulted in a higher MMP-3/TIMP-1 ratio (0.46) than in patients with remission (0.35±0.15). Thus, the total elastolytic activity estimated by the balance between MMPs and TIMPs activities may be high in this patient. In this sense, the MMP-3/TIMP-1 ratio may be a more useful marker for disease activity. Patient 2 had very high CRP levels, but her disease activity score was only 2. This discrepancy may suggest limitations of the NIH criteria for disease activity that do not include CRP as an inflammation marker. However, her circulating MMP-3 level of 191 ng/mL was high enough for diagnosis as active TA. We believe this demonstrates the usefulness of MMP-3 as a disease activity marker. When the cutoff values of 800 and 100 ng/mL were applied for MMP-2 and MMP-3, respectively, the sensitivity was 100% on both determinations. Accordingly, there was no false-positive patient for these 2 markers. As described above, MMP-9 appears to be a less effective marker for disease activity.

Corticosteroids have been shown to increase serum MMP-3 levels in patients with rheumatoid arthritis and other systemic diseases with vasculitides. A possible correlation between steroid therapy and MMP-3 levels was examined in patients in the present study. All patients with active disease and 4 of 14 patients in remission received corticosteroids. Among patients in remission, serum levels of MMP-3 in patients with steroid therapy did not differ from those in patients without steroid therapy (P=0.9468). In addition, MMP-3 levels in steroid-treated patients with active disease were significantly higher than those in 4 steroid-treated patients in remission (P=0.0039). These data suggest that corticosteroids did not have an impact on MMP-3 levels in TA patients.

It was reported that sequential angiographic evaluation, performed regardless of disease activity, identified new lesions in 61% of patients who experienced prolonged remission by clinical criteria and that lesions that initially appeared to respond to glucocorticoid therapy could become progressively stenotic, necessitating vascular bypass procedures. Patients thought to be in clinical remission at the time of surgery could also exhibit histological evidence of inflammation. We speculate that MMP-2 reflects intimal proliferation of mesenchymal cells, such as fibroblasts and smooth muscle cells, in stenotic lesions and that it plays a role in the progression of stenosis, regardless of disease activity. In TA, latent inflammation without manifest exacerbation of the disease may cause stenosis of the affected arteries. After complete resolution from the disease, serum MMP-2 values might be decreased to the levels of healthy controls. In future studies, we plan to determine whether patients with normal MMP-2 levels do not experience vascular stenoses.

In conclusion, the present results suggest that monitoring of circulating levels of MMP-2 as a helpful marker in diagnosing TA and those of MMP-3 and MMP-9 as disease activity markers might help provide adequate evaluation of treatment and guide therapeutic decision making for individual patients with TA. These measurements can be part of routine hospital laboratory examinations that are easy to perform at low cost. Furthermore, the noninvasive nature of such measurements is attractive, because patients can be spared from invasive angiographic examination.

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References

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