Increased Plasma Concentration of Matrix Metalloproteinase-7 in Patients with Coronary Artery Disease

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Background: Plaque rupture is often associated with breakdown of the extracellular matrix in the shoulder region of a plaque. We tested whether plasma concentrations of various matrix metalloproteinases (MMPs) and tissue inhibitor of metalloproteinase-1 (TIMP-1) could serve as markers for plaque instability as well as relationships between plasma MMPs and inflammatory markers.

Methods: The study group included 65 men with angiographically verified CAD (45 with stable and 20 with unstable CAD) and 28 healthy controls. Circulating MMP, TIMP-1, C-reactive protein, and cytokine concentrations were measured by ELISA. Leukocyte subtype counts in whole blood were determined, and T-cell subsets and natural killer cells were measured by flow cytometry. Differences in continuous variables between groups were tested by ANOVA with the Scheffé F-test used as a post hoc test, and correlations were analyzed by a linear regression method.

Results: The plasma concentration of MMP-7 was increased in patients with stable and unstable CAD, whereas MMP-2 and -3 concentrations were decreased. The plasma concentration of TIMP-1 was significantly increased in patients with unstable CAD. MMP-2, -3, and -7 showed no correlations with established markers of inflammation. However, MMP-2 correlated positively with the number of natural killer cells in patients with stable and unstable CAD.

Conclusion: Plasma concentrations of MMPs and TIMPs may be markers of CAD but appear to be differentially regulated.

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Matrix metalloproteinases (MMPs) constitute a family of closely related proteinases that together have the capacity to degrade all components of the extracellular matrix (ECM) (1, 2). MMPs play important roles during physiologic processes such as embryonic development, wound healing, and angiogenesis, but they have also been implicated in several pathologic conditions, such as atherogenesis and precipitation of acute coronary syndromes (ACS) (3). Plaque rupture is often associated with the breakdown of ECM in the shoulder region of a plaque (4, 5). This is supported by the observation that vulnerable plaques, relative to stable plaques, contain low amounts of ECM (6, 7). ECM breakdown is mediated by proteinases, in particular MMPs, which are being overexpressed in the shoulder region of atherosclerotic plaques (3).

Coronary artery disease (CAD) is characterized by focal inflammation of the arterial wall. MMPs and tissue inhibitors of MMPs (TIMPs) are secreted by different cell types of the vessel wall (8–11). The inflammation process modulates the secretion of various MMPs and TIMPs from these cells (3), thereby promoting atherogenesis, plaque rupture, and thrombosis. In conditions of arterial inflammation, such as temporal arteritis, serum or plasma concentrations of MMPs are generally altered (12, 13). It is

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4 Nonstandard abbreviations: MMP, matrix metalloproteinase; ECM, extracellular matrix; ACS, acute coronary syndrome; CAD, coronary artery disease; TIMP, tissue inhibitor of matrix metalloproteinase; UCAD, unstable coronary artery disease; CRP, C-reactive protein; IL, interleukin; NK, natural killer; and apoE, apolipoprotein E.
therefore reasonable to assume that the plasma or serum concentrations of MMPs may reflect MMP activity within the vessel wall.

A few studies have analyzed serum or plasma MMP concentrations in relation to CAD with the focus mainly placed on MMP-9 (14–16). The plasma MMP-9 concentration was recently identified as a novel predictor of cardiovascular mortality in patients with CAD (17). Less attention has been focused on the other MMPs. Similar to MMP-9, MMP-7 is produced in vulnerable regions of the atherosclerotic plaque; however, MMP-7 has a distribution that is distinct from that of MMP-9 in the lesions and also differs in substrate specificity (18). This indicates potentially different roles in plaque destabilization and rupture. Plasma MMP-7 concentrations have not been analyzed previously in patients with CAD. In addition, data suggest that, in contrast to MMP-9, low concentrations of some MMPs may be associated with CAD. In a study of patients with premature stable CAD, the plasma concentration of MMP-9 was found to be increased compared with healthy controls, whereas plasma concentrations of MMP-2 and MMP-3 were decreased (19). However, the existing literature regarding circulating MMP-2 in stable and unstable CAD (UCAD) is conflicting, and it has been shown that serum MMP-2 is increased in patients with stable angina compared with controls and is even further increased in those with ACS (15).

In the present study, we measured the plasma concentrations of MMP-2, -3, and -7 together with their inhibitor TIMP-1 in patients with stable and unstable CAD and tested whether these concentrations correlate with those of C-reactive protein (CRP), cytokines, and immune cells.

**Materials and Methods**

We studied a total of 65 men with angiographically verified CAD; 45 with stable CAD and 20 with UCAD. The patients with stable CAD had effort-related angina (Canadian Cardiovascular Society functional classes I and II) without any worsening of symptoms in the past 6 months (20). Patients with UCAD were eligible for inclusion if they had a diagnosis of unstable angina/non-ST-elevation myocardial infarction on the basis of typical electrocardiographic changes (ST-T-segment depression and/or T-wave inversion) and/or increased troponin T (≥0.03 μg/L). Exclusion criteria were age ≥65 years; diabetes; severe heart failure; immunologic disorders; cancer; evidence of acute or recent (<2 months) infection; recent major trauma, surgery or revascularization procedure; and treatment with immunosuppressive or antiinflammatory agents. Twenty-eight presumably healthy men, recruited from the healthcare staff, served as controls. Blood was obtained by venipuncture in the morning after a 12-h fast. In patients with ACS, blood samples were drawn 1–3 days after onset of symptoms and always before coronary intervention. Informed consent was obtained from all participants. The research protocol was approved by the local ethics committee.

Blood samples were collected in Vacutainer Tubes with or without EDTA and centrifuged within 15 min to separate plasma/serum, which then were stored at −70 °C until analyzed. The MMP and TIMP-1 concentrations in plasma were measured with the Biotrak MMP-2, MMP-3, and TIMP-1 human ELISA systems (Amersham Biosciences) and the Quantikine human MMP-7 ELISA (R & D Systems Europe Ltd.). The assay for TIMP-1 recognizes the total TIMP-1 content, i.e., free TIMP-1 and TIMP-1 complexed with MMPs. Serum interleukin-6 (IL-6) and IL-10 were assayed by high-sensitivity ELISAs (Quantikine HS; R & D Systems Europe Ltd.). Plasma CRP was determined by a highly sensitive latex-enhanced turbidimetric immunoassay (Roche Diagnostics GmbH). The lower limits of detection were 0.37 μg/L (MMP-2), 2.35 μg/L (MMP-3), 0.09 μg/L (MMP-7), 1.25 μg/L (TIMP-1), 0.039 ng/L (IL-6), 0.5 ng/L (IL-10), and 0.1 mg/L (CRP), respectively. The interassay CVs were 6% for MMP-2 (at 6–12 μg/L), 5% for MMP-3 (at 5–10 μg/L), 6% for MMP-7 (at 0.6–1.0 μg/L), 5% for TIMP-1 (at 7–15 μg/L), 8% for IL-6 (at 0.3–2 ng/L), and 7% for IL-10 (at 0.7–4.5 ng/L). The CVs for CRP were 2% and 11% at 14 and 0.7 mg/L, respectively.

We determined the distribution of peripheral blood mononuclear cells by 3-color flow cytometry using FACS-Scan (Becton Dickinson Immunocytometry Systems), as described previously (21). Data were analyzed by use of CELL Quest software (Becton Dickinson).

Statistical analyses were performed with StatView software (SAS). Differences in continuous variables between groups were tested by ANOVA with the Scheffé F-test used as a post hoc test. Skewed data (IL-6, CRP, and MMP-3) were log-transformed to a gaussian distribution before comparisons were made. Correlations were analyzed by a linear regression method. For analysis of correlation, patients with stable CAD and UCAD were combined. Two-tailed P values <0.05 were considered as statistically significant.

**Results**

The baseline data are summarized in Table 1. All patients were receiving various combinations of beta blockers, calcium antagonists, and nitrates. In addition, all patients with UCAD were receiving low–molecular-weight heparin and clopidogrel.

Patients with UCAD had higher leukocyte counts than patients with stable CAD and controls (Table 1). This difference was accounted for by higher monocyte and neutrophilic granulocyte counts. In addition, the CRP and IL-6 concentrations were significantly higher in patients with UCAD than in patients with stable CAD and in controls. Furthermore, there was a nonsignificant trend toward lower natural killer (NK)-cell counts in patients with CAD compared with controls. The number of T cells, T-helper cells, and T-cytotoxic cells did not differ among the groups (data not shown).
Plasma concentrations of MMPs and TIMP-1 are also shown in Table 1. The controls had plasma concentrations within the reference intervals provided by the manufacturer. Plasma concentrations of MMP-2 were significantly decreased in patients with UCAD compared with patients with stable CAD and healthy controls. Similarly, plasma concentrations of MMP-3 were 3-fold higher in the control group than in the group of UCAD patients, with the plasma concentrations of stable CAD patients being intermediate. Conversely, MMP-7 concentrations were increased by 50% and 60% in the unstable and stable CAD groups, respectively, compared with controls. TIMP-1 concentrations were higher in patients with UCAD than in controls. Adjustment for age, smoking habits, and body mass index did not influence the results for MMPs and TIMP-1.

In the group of UCAD patients, we found no difference in plasma concentrations of any MMP or TIMP-1 when we compared troponin T-positive (≥0.03 μg/L) and troponin T-negative (<0.03 μg/L) individuals within the group. Furthermore, we found no differences in plasma concentrations of MMPs or TIMP-1 when we compared patients receiving or not receiving statin medication in both the stable and unstable CAD groups.

The plasma TIMP-1 concentrations showed positive correlations with the leukocyte count and the number of neutrophilic granulocytes in blood in the patient group (Table 2), but not in the control group. Plasma MMP-2, -3, and -7 concentrations showed no correlation with the number of leukocytes or neutrophilic granulocytes, nor were there any correlations between the total number of

### Table 1. Basic characteristics and plasma MMP and TIMP-1 concentrations in healthy controls and patients with stable and unstable CAD.

<table>
<thead>
<tr>
<th>Group</th>
<th>Healthy controls</th>
<th>Stable CAD</th>
<th>UCAD</th>
<th>Unadjusted</th>
<th>Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>28</td>
<td>45</td>
<td>20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD) age, years</td>
<td>52.5 (5.7)</td>
<td>57.4 (4.7)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>55.8 (6.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking, %</td>
<td>14</td>
<td>31</td>
<td>60</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD) BMI, kg/m&lt;sup&gt;2&lt;/sup&gt;</td>
<td>24.9 (2.7)</td>
<td>27.5 (2.8)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>26.1 (3.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD) serum triglycerides, mmol/L</td>
<td>1.57 (1.21)</td>
<td>2.01 (0.98)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2.80 (1.61)&lt;sup&gt;d&lt;/sup&gt;&lt;sup&gt;g&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD) serum cholesterol, mmol/L</td>
<td>5.86 (0.94)</td>
<td>5.09 (0.86)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>5.39 (1.08)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD) blood pressure, mmHg</td>
<td>Systolic</td>
<td>128 (13)</td>
<td>140 (18)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>131 (24)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diastolic</td>
<td>81 (5)</td>
<td>83 (9)</td>
<td>80 (13)</td>
<td></td>
</tr>
<tr>
<td>Troponin T-positive,&lt;sup&gt;h&lt;/sup&gt; %</td>
<td>50</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical treatments, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statins</td>
<td>0</td>
<td>78</td>
<td>65</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>0</td>
<td>91</td>
<td>100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD) cell counts, cells/μL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total leukocytes</td>
<td>5800 (1200)</td>
<td>6400 (1400)</td>
<td>7400 (1500)&lt;sup&gt;h&lt;/sup&gt;&lt;sup&gt;g&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>1900 (500)</td>
<td>2100 (600)</td>
<td>2000 (700)</td>
<td></td>
<td></td>
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<tr>
<td>Monocytes</td>
<td>600 (200)</td>
<td>600 (200)</td>
<td>1000 (1200)&lt;sup&gt;h&lt;/sup&gt;&lt;sup&gt;g&lt;/sup&gt;</td>
<td></td>
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<tr>
<td>Neutrophils</td>
<td>3100 (700)</td>
<td>3500 (1000)</td>
<td>4400 (1300)&lt;sup&gt;h&lt;/sup&gt;&lt;sup&gt;n&lt;/sup&gt;</td>
<td></td>
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<tr>
<td>Mean (SD) plasma concentrations</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>CRP, mg/L</td>
<td>1.5 (1.2)</td>
<td>4.1 (5.8)</td>
<td>18.5 (31.9)&lt;sup&gt;h&lt;/sup&gt;&lt;sup&gt;n&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL-6, ng/L</td>
<td>1.8 (1.0)</td>
<td>4.1 (3.8)</td>
<td>9.4 (13.9)&lt;sup&gt;h&lt;/sup&gt;&lt;sup&gt;n&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL-10, ng/L</td>
<td>2.4 (2.5)</td>
<td>2.8 (2.40)</td>
<td>2.1 (1.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMP-2, μg/L</td>
<td>872 (156)</td>
<td>882 (127)</td>
<td>683 (139)&lt;sup&gt;d&lt;/sup&gt;&lt;sup&gt;i&lt;/sup&gt;</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MMP-3, μg/L</td>
<td>18.6 (11.7)</td>
<td>10.0 (7.4)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>4.9 (3.8)&lt;sup&gt;d&lt;/sup&gt;&lt;sub&gt;l&lt;/sub&gt;</td>
<td>&lt;0.0001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MMP-7, μg/L</td>
<td>3.2 (1.5)</td>
<td>5.2 (2.1)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>5.0 (2.4)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>&lt;0.001</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>TIMP-1, μg/L</td>
<td>858 (91)</td>
<td>921 (138)</td>
<td>1085 (201)&lt;sup&gt;c&lt;/sup&gt;&lt;sup&gt;d&lt;/sup&gt;&lt;sub&gt;i&lt;/sub&gt;</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

<sup>a</sup> ANOVA comparing all groups. Adjusted P: adjusted for age, smoking, and body mass index.
<sup>b–e</sup> Compared with controls: <sup>b</sup> P <0.001; <sup>c</sup> P <0.05; <sup>d</sup> P <0.0001; <sup>e</sup> P <0.01.
<sup>f</sup> BMI, body mass index.
<sup>g–j</sup> Compared with patients with stable CAD: <sup>g</sup> P <0.05; <sup>h</sup> P <0.01; <sup>i</sup> P <0.0001; <sup>j</sup> P <0.001.
<sup>k</sup> Troponin T ≥0.03 μg/L.

### Table 2. Correlations between plasma TIMP-1 concentrations and markers of inflammation in patients with CAD (n = 65).

<table>
<thead>
<tr>
<th>TIMP-1</th>
<th>Leukocyte count</th>
<th>Neutrophilic granulocytes</th>
<th>IL-6</th>
<th>High-sensitivity CRP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Correlation coefficient (r)</td>
<td>0.30</td>
<td>0.34</td>
<td>0.58</td>
<td>0.46</td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.05</td>
<td>&lt;0.01</td>
<td>&lt;0.0001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
lymphocytes in blood and plasma concentrations of any of the MMPs or TIMP-1.

MMP-2 was negatively correlated with the total number of T cells ($r = -0.45; P < 0.05$), the number of T-helper cells ($r = -0.45; P < 0.05$), and the number of T-helper cells expressing IL-2R ($r = -0.48; P < 0.01$) in controls, whereas we found no correlations in the patient group. MMP-2 concentrations were positively correlated with NK-cell count in the patient group ($r = 0.26; P < 0.05$), but not in controls. Plasma concentrations of MMP-3, MMP-7, and TIMP-1 were not correlated with any of the T-cell subsets or with NK-cell count.

We analyzed the CRP and cytokine measurements in relation to plasma MMP and TIMP-1 concentrations. In the CAD patients, but not in the controls, TIMP-1 was strongly positively correlated with IL-6 and CRP (Table 2). MMP-2 and MMP-3, on the other hand, showed no significant correlations with any of the cytokines, whereas MMP-7 was weakly but significantly correlated with IL-10 ($r = 0.26; P < 0.05$) in the CAD patients but not in the controls.

**Discussion**

We analyzed the plasma concentrations of several MMPs and TIMP-1 in patients with stable and unstable CAD and in healthy controls and found significant differences in plasma concentrations between the groups for MMP-2, MMP-3, MMP-7, and TIMP-1. Importantly, plasma MMP-7 concentrations were significantly increased in patients, whereas MMP-2 and MMP-3 concentrations were significantly lower. This suggests that the various MMPs might play different roles in CAD. This is not unexpected because different MMPs have been shown to be involved in many cellular processes, such as smooth muscle cell migration, release of growth factors, angiogenesis, and ECM degradation, processes that may have different effects on cardiovascular disease (22–24). Divergent effects of different MMPs on the atherosclerotic process have been suggested by recent studies in MMP-deficient mouse models. Johnson et al. (25) studied the effects of MMP-3 and MMP-7 on atherosclerosis by comparing apolipoprotein E (apoE)/MMP-3 double-knockout mice with apoE/MMP-7 mice. The smooth muscle cell content in plaques was decreased in apoE/MMP-3 double-knockout mice compared with apoE single-knockout controls. The opposite was found for the apoE/MMP-7 double-knockout mice. Furthermore, plaque areas were larger for the apoE/MMP-3 double-knockout mice, whereas there was no significant difference in plaque areas between the apoE/MMP-7 mice and control mice. These findings support the notion that MMP-7 may be protective for atherosclerotic lesion development. In the present study, we found no evidence that the altered plasma MMP concentrations reflect altered MMP production in plaques.

The present study showed an association between MMP-7 and CAD. MMP-7 was increased equally in patients with stable and unstable CAD. The plasma MMP-7 concentration was unrelated to all markers of inflammation, which suggests that plasma MMP-7 might be a marker of atherosclerosis that is independent of the traditional inflammatory markers.

In contrast to MMP-7, plasma MMP-3 was significantly decreased in the patients with stable CAD and was even lower in the group with UCAD. This is in accordance with 2 recent studies (19, 26). In addition, we have recently demonstrated that the serum MMP-3 concentration is significantly lower in the acute phase of myocardial infarction than during recovery (27). MMP-7, -8, -9, and -13 can all be inactivated by MMP-3 (2). Thus, decreased plasma concentrations of MMP-3, as seen in CAD patients, might indicate increased ECM degradation and enhanced risk of plaque rupture promoted by other MMPs.

Similarly to MMP-3, in our study, the plasma MMP-2 concentration was decreased in individuals with UCAD compared with controls and patients with stable CAD. Two previous studies of MMP-2 in relation to CAD have given conflicting results (19, 28). Part of this discrepancy might be explained by differences in the baseline characteristics of the study populations. The MMP-2 concentration correlated positively with the number of NK cells in CAD patients. The number of NK cells is lower and NK-cell activity is impaired in patients with chronic immunologic diseases (29) and decreased NK-cell function has been associated with atherosclerosis in elderly humans (30). Indeed, we found that decreased concentrations of MMP-2 were associated with low numbers of NK cells in patients with CAD.

In agreement with a previous study (19), in our study the plasma TIMP-1 concentration was increased in patients with CAD. Recently, Lubos et al. (31) demonstrated that high serum TIMP-1 is a risk predictor for future cardiovascular death. The assay used in the present study recognizes the total TIMP-1 content, i.e., free TIMP-1 and TIMP-1 complexed with MMPs. Thus, increased plasma TIMP-1 in patients with stable and unstable CAD could reflect increased matrix-degrading activity with accumulation of MMP–TIMP-1 complexes in plasma. The plasma TIMP-1 concentration correlated strongly with markers of inflammation, such as IL-6 and CRP, in patients with manifest CAD. In the UCAD group, variations in the time point of blood sampling and extent of troponin T increase could explain part of the wide variability in CRP and IL-6 values. However, the observed correlation between TIMP-1 and these inflammatory markers could not be explained merely by a correlation between TIMP-1 and development of myocardial necrosis, because plasma TIMP-1 concentrations did not differ between troponin T-positive and -negative patients in the UCAD group. TIMP-1 also showed positive correlations with the leukocyte count and the number of neutrophilic granulocytes in CAD patients.

The members of the 3 study groups differed in some
baseline characteristics. These differences among the groups could explain some of the differences seen in MMP and TIMP-1 concentrations. However, when we adjusted for age, body mass index, and smoking, differences in plasma MMP and TIMP-1 concentrations remained. Furthermore, the majority of patients with either stable and unstable CAD were receiving statin treatments. Statins have been shown to alter the production of various MMPs both in vivo and in vitro (32–34), and it is likely that statin medication could have also influenced plasma concentrations of MMPs and TIMP-1 in the present study. In their study, Furman et al. (34) demonstrated that rosuvastatin decreases the secretion of MMP-7 from human macrophages in vitro. Whether statin treatment lowers plasma MMP-7 concentrations is not known. If it does, however, that effect would act to diminish the differences between patients and controls observed in the present study. In addition, we found no difference in plasma concentrations for any of the MMPs or TIMP-1 when we compared patients receiving or not receiving statin treatment in both the stable and the unstable CAD groups.

In summary, plasma concentrations of MMPs and TIMPs may be important markers of CAD. Prospective studies are needed to demonstrate whether plasma MMP concentrations can be used as independent predictors of different manifestations of atherosclerotic disease.

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