Diagnostic utility of serum MMP-9 and plaque progression in patients of the acute coronary syndrome: A tertiary care hospital based study

Keshav Kale¹, Deepali Vidhate², Ghanashyam Kane³
¹Assistant Professor, ²Professor, ³Professor and Head
Department of Cardiology¹,³, Department of Biochemistry²
School of Medicine, D Y Patil Deemed to be University, Nerul, Navi Mumbai, India

Corresponding Author:
Deepali Vidhate
Professor, Department of Biochemistry, School of Medicine, D Y Patil Deemed to be University, Nerul, Navi Mumbai, India

Type of Publication: Original Research Paper
Conflicts of Interest: Nil

ABSTRACT
Matrix metalloproteinases (MMPs) are proteases which play an important role in extracellular matrix remodeling. During plaque progression macrophages and mast cells secrete matrix-degrading proteolytic enzymes MMPs. These are involved in the process of atherogenesis and play an important role in plaque destabilization, which is the most widespread mechanism for Acute Coronary Syndrome. Tissue proteolysis is associated with thinning and rupturing of atherosclerotic fibrous cap. High MMP-9 levels can serve as a predictor of atherosclerotic plaque vulnerability. The aim of the present study is to compare the association of MMP-9 with degree of ACS. Results: Serum levels of MMP-9 were significantly higher in the STEMI group than of NSTMI and unstable angina group. Significant positive correlations were found between MMP-9 and HsCRP as well as markers of myocardial necrosis. Conclusion: In conclusion, MMP-9 could be considered as an early risk marker for identification of patients with ACS. MMP-9 may be a potential target for preventing atherosclerotic plaque vulnerability.

Keywords: Inflammation, ACS, Unstable Angina, NSTEMI, STEMI and MMP-9.

INTRODUCTION
Atherosclerosis is an inflammatory process in which subclinical patho-physiological changes initiates much before the onset of clinical symptoms. Pro-inflammatory biomolecules play an important role in setting inflammation which initiates multiple inflammatory cascades and ultimately results in atherogenesis - plaque formation in coronary artery [1, 2]. Destabilization of plaques might results in fatal events and found to be associated with matrix metalloproteinases (MMPs) activity as they play an important role in degradation of extracellular matrix (ECM). MMP-9 degrades Extra Cellular Matrix (ECM) proteins and activates cytokines and chemokines to control tissue remodeling. Destabilization of plaque further leads to plaque rupture and eventually a fatal Acute Coronary Syndrome (ACS) event. Proinflammatory mediators also stimulates the activity MMPs [3]. MMP-9 enhances endothelial dysfunction and favors the migration of leukocytes and inflammatory mediators [4] which has been identified as a key event in development and progression of plaques.

MMP-9, also called as gelatinase B, an enzyme which is involved in degradation of type IV collagen and elastin [5]. MMP-9 is known to be synthesized by Neutrophils, macrophages, endothelial cells, and smooth muscle cells and various other cell types. Studies reported elevated circulatory MMP-9
concentrations in ACS patients and stable CAD patients [11–13]. It has been also observed that as compared to stable angina circulatory levels of MMP-9 were associated with vulnerable plaques and plaque rupture [14]. In the present study, we determined serum MMP-9 levels in ACS patients. The aim of the present study is to compare the association of MMP-9 activation and degree of ACS.

**Materials and Methods**

The present study was carried out at D Y Patil University Hospital, Navi Mumbai. The 102 patients included 42 unstable angina patients, 29 Non S T segment MI (NSTEMI) and 31 ST Elevation MI patients.

The inclusion criteria for both cases and controls were age under 75 years, no cognitive intellectual disability, and no operations or chemotherapy. Venous blood sample was collected.

The diagnosis was based on the clinical symptoms, biochemical investigations and electrocardiogram (ECG). AMI was diagnosed on the basis of the following criteria: chest pain related to exercise lasting over 20 min or changes in ECG, such as ST-elevations followed by T-wave inversion or new Q-waves, or an increase in Creatine kinase-MB (CK-MB) to more than twice the upper limit of the normal value (>5 μg/l). UAP was diagnosed if two of following criteria were fulfilled: continuous chest pain, ST-segment depression in the ECG (<1 mm), or elevation of CK-MB (5<CK-MB<10 μg/l) or troponin T (0.05<TnT<0.10 μg/l).

Total 110 controls were age and sexes matched and were without previous coronary heart disease, stroke, or angina-like chest pain and were not taking medication for dyslipidemia, hypertension, or diabetes. Fasting venous blood samples were collected, in a plain test tube without anticoagulant. Samples for measurement of MMP-9 were collected immediately after hospitalization from patients for whom the symptom complex was consistent with ACS till diagnosis was established (mainly within the first 4 hours from the start of chest pain) and the serum was stored at −20°C in duplicates until analysis.

**Results:** The clinical and biochemical parameters were performed. Other conventional risk factors normal. The present study reported high levels of MMP-9 in ACS patients as compared to controls.

Patients with ACS did not show significantly higher WHR and higher LDL compared to healthy controls. While various other parameters were near to normal in ACS patients. Levels of MMP-9 were significantly elevated among all patients with ACS compared to healthy controls. The highest levels were found among STEMI followed by NSTEMI than unstable angina patients.

**Discussion:**

The present study reported a similar observation in consistence with previous studies about the circulatory levels of MMP-9 and its association with ACS. Some studies observed that plasma MMP-9 levels were associated with CVD mortality in patients with CAD at baseline [16, 23]. The present study results showed a strong association of AMI and higher circulatory levels of MMP-9. Previous studies have also suggested that elevated MMP-9 is associated with higher risk of death with CVD risk factors and total cardiovascular risk in subjects without cardiovascular clinical symptoms of CAD [25].

The study reports showed that serum MMP-9 concentrations were linked with both AMI and UAP, which supported the former study findings [14]. It has been also observed that MMP-9 levels were elevated at a faster rate in patients with STEMI than non-STEMI than those of early cardiac damage markers like [27], high-sensitivity troponin T. Further it was seen that the MMP-9 levels correlated with plaque rupture. The duration investigation of plasma MMP-9 has been shown to have a great impact on circulatory MMP-9. It has been also observed that investigation of MMP-9 levels immediately after the cardiac event provides the highest values of circulatory MMP-9 which were always associated with the severity of damage. Myocardium-specific markers CK-MB and troponin T shows a significant correlation with MMP-9 signifying a source of systemic MMP-9 secretion by ischemic myocardial tissue, after an ACS event. Myocardial damage can influence MMP expression and activation [29]. Cytokines and additional pro-inflammatory mediators boost the synthesis and secretion of MMP-9 from inflammatory cells [3]. CRP increases MMP-9 expression in smooth muscle cells in a dose-
dependent manner and correlates with MMP-9 levels in ACS patients [30]. This correlation was also observed in the present study. Serum MMP-9 may reflect a systemic inflammatory state [1], but genetic variation may also contribute to the MMP-9 levels and activity [31] and thereby to the risk of coronary artery disease [32].

Serum MMP-9 determination will stand as an intense and distinct biochemical marker in clinical practice. MMP-9 plays a dual role in atherosclerotic plaque rupture and tissue destruction after a cardiac event. The circulatory levels of MMP-9 may provide an insight for disease related diagnostic severity and its utility for progression of the disease.

Clinical Relevance

MMP-9 can be utilized as an early stage biomarker, because its elevation reflects atherosclerotic plaque rupture and myocardial tissue destruction. Furthermore, MMP-9 has prognostic value, which is important in secondary prevention and planning of personalized treatment.

High levels of MMP-9 were strongly associated with disease severity and the degree of ACS complications. Further cohort studies with follow-up and successive measurement of MMP-9 throughout the course of treatment are needed.

References:


5. Van Doren SR. Matrix metalloproteinase interactions with collagen and elastin. Matrix Biology. 2015;44-46:224–231. doi: 10.1016/j.matbio.2015.01.005. [PMC free article] [PubMed] [CrossRef] [Google Scholar]


11. Pesonen E, El-Segaier M, Persson K, Puolakkainen M, Sarna S, Ohlin H, Pussinen PJ. Infections as a


Tables:

**Table 1: Descriptive statistics for ACS and Control groups**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ACS Mean(S.D.±)</th>
<th>Control Mean(S.D.±)</th>
<th>‘p’ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAG (mg %)</td>
<td>172.3(±36.21)</td>
<td>142.94(±20.23)</td>
<td>0.00</td>
</tr>
<tr>
<td>Cholesterol (mg %)</td>
<td>185.56(±27.56)</td>
<td>160.5(±20.21)</td>
<td>0.00</td>
</tr>
<tr>
<td>VLDL (mg %)</td>
<td>35.41(±8.2)</td>
<td>30.61(±10.05)</td>
<td>0.00</td>
</tr>
<tr>
<td>LDL (mg %)</td>
<td>102.3 (±16.4)</td>
<td>82.61(±22.49)</td>
<td>0.00</td>
</tr>
<tr>
<td>HDL (mg %)</td>
<td>42.33 (±5.32)</td>
<td>49.5(±6.28)</td>
<td>0.00</td>
</tr>
<tr>
<td>BMI</td>
<td>26.61(±1.32)</td>
<td>24.16(±1.82)</td>
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<tr>
<td>WC (cm)</td>
<td>86.23(±6.35)</td>
<td>84.39(±4.7)</td>
<td>0.00</td>
</tr>
<tr>
<td>Waist hip ratio</td>
<td>0.94(±0.06)</td>
<td>0.90(±0.05)</td>
<td>0.00</td>
</tr>
<tr>
<td>FBS (mg %)</td>
<td>137.54(±58.3)</td>
<td>100.44(±10.70)</td>
<td>0.00</td>
</tr>
<tr>
<td>MMP-9(ng/ml)</td>
<td>338.47 (±204.5)</td>
<td>150.25(±90.3)</td>
<td>0.00</td>
</tr>
</tbody>
</table>

**Table 2: MMP-9 levels and subgroups of ACS and Control**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>MMP-9 Mean(S.D.±)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unstable MI</td>
<td>330.28 (±202.5)</td>
</tr>
<tr>
<td>NSTEMI</td>
<td>339.56 (±188.4)</td>
</tr>
<tr>
<td>STEMI</td>
<td>345.59 (±210.5)</td>
</tr>
<tr>
<td>Control</td>
<td>150.25 (±90.3)</td>
</tr>
</tbody>
</table>