

Serum Matrix Metalloproteinase-9 Levels in Acute Coronary Syndrome Patients with and without Hyperglycemia

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ABSTRAK

Tujuan: untuk mengetahui perbedaan kadar matrix metalloproteinase-9 (MMP-9) serum pada pasien sindroma koroner akut dengan dan tanpa hiperglikemia. **Metode:** desain penelitian ini merupakan potong-lintang pada pasien dengan sindroma koroner akut yang dirawat di ICCU Rumah Sakit Dr. Sardjito Yogyakarta Indonesia. Pencuplikan subjek dilakukan secara berurutan. Pengukuran kadar glukosa darah dilakukan saat masuk rumah sakit dan MMP-9 dilakukan sesaat setelah tiba di ICCU. Glukosa darah >140 mg/dL ditetapkan sebagai hiperglikemia. Uji Student t digunakan untuk menganalisis perbedaan kadar MMP-9 antara subjek dengan dan tanpa hiperglikemia. **Hasil:** dari 72 subjek penelitian, 34 subjek dengan hiperglikemia dan 38 subjek tanpa hiperglikemia. Rerata kadar glukosa darah berbeda signifikan antara subjek dengan dan tanpa hiperglikemia (204,4±92.16 vs. 108,93±19,1 mg/dL, p=0,0001). Rerata kadar MMP-9 pada subjek dengan hiperglikemia secara signifikan lebih tinggi daripada subjek tanpa hiperglikemia (1574±573,61 ng/mL vs. 1370±573,66 ng/mL, p=0,025). Rasio prevalensi MMP-9 tinggi diantara subjek dengan hiperglikemia mencapai 2,88 (95% CI: 1,16–7,14), p=0.004. **Kesimpulan:** kadar MMP-9 serum pada pasien sindroma koroner akut dengan hiperglikemia secara signifikan lebih tinggi dibandingkan pasien tanpa hiperglikemia.

Kata kunci: sindrom koroner akut, matriks metaloproteinase-9, hiperglikemia.

ABSTRACT

Aim: to determine the difference in serum matrix metalloproteinase-9 (MMP-9) levels among acute coronary syndrome patients with and without hyperglycemia. **Methods:** this study was a cross-sectional study on patients with acute coronary syndrome admitted to ICCU of Dr. Sardjito Hospital Yogyakarta Indonesia. Measurements of blood glucose level were performed on hospital admission, while measurement of MMP-9 level was performed upon arrival at the ICCU. Hyperglycemia was defined as a random blood glucose level of >140 mg/dL. Student's t test was performed to analyze the difference of MMP-9 level between subjects with and without hyperglycemia. **Results:** of 72 enrolled subjects, there were 34 subjects with hyperglycemia and 38 subjects without hyperglycemia. The mean blood glucose level was significantly different in subjects with hyperglycemia as compared to those without hyperglycemia (204.4±92.16 vs. 108.93±19.1 mg/dL, p=0.0001). The mean MMP-9 level in subjects with hyperglycemia was significantly higher than those without hyperglycemia (1574±573.61 vs. 1370±573.66 ng/mL, p=0.025). The prevalence ratio of high MMP-9 level among subjects with hyperglycemia was 2.88 (95% CI: 1.16-7.14), p=0.004. **Conclusion:** serum MMP-9 level in patients suffering from acute coronary syndrome with hyperglycemia was significantly higher than those without hyperglycemia.

Key words: acute coronary syndrome, matrix metalloproteinase-9, hyperglycemia.

INTRODUCTION

Previous studies have demonstrated that hyperglycemia is often found upon hospital admission in patients with acute coronary syndrome. Hyperglycemia is one of the risk factors for mortality and complications during hospitalization.^{1,2} Despite the varied definitions of hyperglycemia, the prevalence of hyperglycemia in acute coronary syndrome ranges from 25% to 50%.¹⁻³ Increased long-term mortality and larger infarct size in patients with acute myocardial infarction have been associated with in-hospital hyperglycemia. Previous diabetes mellitus is also a risk factor for developing hyperglycemia during episodes of acute coronary syndrome.⁴

Coronary heart disease causes myocardial ischemia with diverse clinical spectrums, namely ischemia without symptoms (silent ischemia), stable angina pectoris, acute coronary syndrome, heart failure and sudden cardiac death. Atherosclerosis is the underlying pathology in acute coronary syndromes.⁵ Pathophysiology of coronary atherosclerosis involves an inflammation process. A number of inflammatory biomarkers have been investigated in association with plaque instability, one of which is matrix metalloproteinase (MMP) system.⁶

MMP are proteolytic enzymes which cause degradation of the extracellular matrix, resulting in tissue remodeling during normal biological processes. Vascular remodeling is now recognized as a major determinant for vascular pathologies including atherosclerosis and restenosis. It is widely accepted that the dysregulation of the MMP system plays an important role in vascular remodeling and atherosclerosis.⁷ Furthermore, MMP system is increased in vascular wall of diabetic patients which implies that chronic hyperglycemia may induce MMP-mediated atherosclerosis.⁸

Among MMPs, MMP-9 plays an important role in the degradation of extracellular matrix. Its activity is increased during rupture of atherosclerotic plaques which causes acute coronary syndrome.⁹ In patients with acute coronary syndrome, serum MMP-9 levels elevates in coronary and systemic circulation.⁹ On the other hand, acute hyperglycemia is frequently found in acute coronary syndrome.^{1,2}

Acute hyperglycemia may induce elevated MMP expression in large vessels due to its effect on oxidative stress and RAGE production.¹⁰ Previous study showed reduced serum MMP-9 levels among diabetic patients.¹¹ However the impacts of acute hyperglycemia, such as in acute coronary syndrome, on serum MMP levels have not yet been established.

Our study was conducted to determine whether there were differences of serum MMP-9 levels among patients suffering from acute coronary syndrome with and without hyperglycemia.

METHODS

The study was a cross-sectional study conducted at Dr. Sardjito Hospital, Yogyakarta Indonesia. Target population of the study was patients suffering from acute coronary syndrome with hyperglycemia (random blood glucose levels of >140 mg/dL) and without hyperglycemia (random blood glucose levels of ≤140 mg/dL) who were hospitalized at the ICCU. Cut-off value for random blood glucose levels was in accordance with previous publication.¹² Subjects were enrolled consecutively.

Inclusion criteria of our study were: (1) patients with acute coronary syndrome, including those with ST elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMI) and unstable angina pectoris (UAP); (2) the onset of symptom ≤24 hours; (3) male and female patients with age of >20 years and (4) patients who agreed to participate in the study by signing the informed consent form. Exclusion criteria of the study were: (1) patients with chronic renal failure requiring renal replacement therapy, chronic congestive heart failure, liver cirrhosis, previous heart valve disease, acute stroke, acute complications of diabetes mellitus, acute exacerbation of chronic obstructive pulmonary disease, pneumonia, sepsis, chronic inflammatory disease, venous thromboembolic disease and malignancy, and (2) pregnant women.

The study was approved by The Ethical Committee of Faculty of Medicine, Universitas Gadjah Mada, Yogyakarta, Indonesia.

Diagnostic and Laboratory Examination

Diagnosis of acute coronary syndrome was established based on the diagnostic criteria of acute coronary syndrome, i.e. the typical chest pain, ST-T changes on 12 ECG leads, and presence or absence of elevated levels of CKMB and/or troponin I. Clinical and demographic data were recorded in the case report form upon hospital admission. Blood sampling for standard laboratory tests, including glucose level, were taken in the emergency room upon hospital admission. Laboratory tests were carried out in the Clinical Pathology Laboratory, Dr. Sardjito Hospital. Blood sampling for MMP-9 levels measurement were taken at the ICCU on the first day of arrival. Blood samples were withdrawn from the forearm in the supine position with a vacutainer, which allowed the blood to clot and be extracted for its serum. The sample was then centrifuged and the supernatant was stored at -80°C , until it was ready for the MMP-9 assay. Examination of MMP-9 was conducted by ELISA methods with a Quantikine Human MMP-9 Immunoassay (R & D Systems, Minneapolis, USA).

Statistical Analysis

Characteristics of subjects were described in mean value and standard deviation (SD) or median (minimal – maximal value) for continuous data based on the data distribution pattern. To analyze differences in mean value between two groups, we used Student's T test or Mann-Whitney U Test. The data were analysed for normality with Shapiro-Wilk test. Categorical data were presented in proportion. To evaluate the difference in proportion among both groups, we used chi-squared test or Fisher's Exact Test. A statistical significance was set at $p < 0.05$.

RESULTS

There were 72 subjects with acute coronary syndrome enrolled in the study. Among them, 34 subjects had hyperglycemia whereas 38 subjects had no hyperglycemia. The mean age of all subjects was 57.66 years, there was no significant difference of ages between subjects with and without hyperglycemia. The majority of subjects were males and accounted for almost 90% of all subjects. Ninety subjects (26.4 %) had diabetes

mellitus, 47 subjects (65.3 %) had dyslipidemia, 44 subjects (61.1%) had hypertension and 22 subjects (30.6 %) were active smokers.

The median value of serum MMP-9 levels in all subjects was 1289 ng/mL. Furthermore, the mean value of MMP-9 levels in subjects with hyperglycemia was 1574 ± 573.61 ng/mL; while in subjects without hyperglycemia, the mean MMP-9 levels was lower, i.e. 1370 ± 573.66 ng/mL. The difference was statistically significant ($p = 0.02$) (Table 1).

To determine the cut-off value of MMP-9 levels for predicting hyperglycemia, we used the Receiver Operator Characteristic (ROC) curve analysis. From the ROC curve (Figure 1), we found that the cut-off value of MMP-9 levels was best fitted at 1014.25 ng/mL, which gave a sensitivity of 88.2%, specificity of 59.2% and area under the curve (AUC) of 65%.

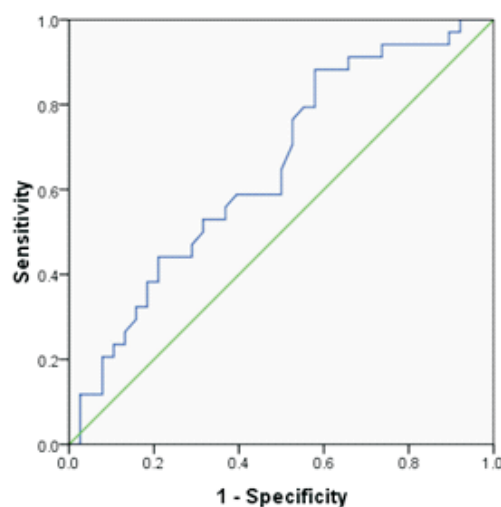


Figure 1. ROC curve to determine the cut-off value of MMP-9

Based on the cut-off value for MMP-9 level, the subjects were categorized into 2 groups, i.e. those with high MMP-9 levels who had the levels above the cut-off value (52 subjects) and those with low MMP-9 levels, who had the levels under the cut-off value (20 subjects). The proportion of high MMP-9 levels among subjects with hyperglycemia was significantly higher compared to the proportion among those without hyperglycemia ($p = 0.004$). High MMP-9 level was associated with hyperglycemia, which

contributed to prevalence ratio of 2.88 (95% CI: 1.16-7.14), $p=0.004$. (**Table 2**)

DISCUSSION

Our study result showed that the MMP-9 levels were significantly higher among patients with acute coronary syndrome who also had increased blood glucose levels. Furthermore, the serum MMP-9 levels were found to be almost three times higher in patients with hyperglycemia

than those with normal blood glucose levels. The result highlighted the notion that blood glucose levels may affect the release of MMP-9 from ruptured atherosclerotic plaque.

Previous study has indicated that there is an increased MMP-9 levels in patients with acute coronary syndrome compared to healthy people.¹³ A study by Garvin et al.¹⁴ showed that MMP-9 levels increased in individuals with dyslipidemia, obesity, diabetes mellitus, smoking, alcohol

Table 1. Characteristics of the subjects

Characteristics	All Subjects (n=72)	With Hyperglycemia (n=34)	Without Hyperglycemia (n=38)
Age (years)	57.66±10.87	57.31±11.6	57.69±10.44
Sex, n(%)			
- Male	64 (88.9)	31 (91.1)	33 (86.8)
- Female	8 (11.1)	3 (8.9)	5 (13.1)
Diagnosis, n(%)			
- STEMI	38 (52.8)	22 (64.7)	16 (42.1)
- NSTEMI	15 (20.8)	5 (14.7)	10 (26.3)
- UAP	19 (26.4)	7 (20.6)	12 (31.6)
Previous disease, n(%)			
- Hypertension	44 (61.1)	21 (61.7)	23 (60.5)
- Dyslipidemia	47 (65.3)	23 (67.6)	24 (63.1)
- Diabetes mellitus	19 (26.4)	17 (50)	2 (5.2)
- Stable Angina Pectoris	20 (27.8)	6 (17.6)	14 (36.8)
Smoking, n(%)			
- Smoking	22 (30.6)	12 (35.3)	10 (26.3)
- Non smoking	13 (18.1)	6 (17.6)	7 (18.4)
- Ex Smoker	37 (51.4)	16 (47.1)	21 (55.3)
Killip class , n(%)			
- Killip I	61 (84.7)	27 (79.5)	34 (89.5)
- Killip II-IV	11 (15.3)	7 (20.5)	4 (10.5)
Body mass index (kg/m ²)	22.54(18.36-33.79)*	23.07±2.28	23.48±3.26
Onset (hour)	5 (1.5-24)*	7.03±6.12	7.44±7.11
Blood pressure (mmHg)			
- Systolic	129.52±28.08	128.78±26.4	128.2±30.77
- Diastolic	78±15.66	76.8±15.7	79.1±16.36
Glucose (mg/dL)	139 (48-604)*	204.4±92.16	108.93±19.1
MMP-9 (ng/mL)	1289 (335.7-2556)*	1574±573.61	1370±573.66
Creatinine (mg/dL)	1.19 (0.47-7.5)*	1.4±0.62	1.5±1.23
Cholesterol (mg/dL)	197.56±50.77	202.8±56.75	195.7±44.2
LDL (mg/dL)	125.5 (53-291)*	125±47.03	127.73±40.8
Triglyceride (mg/dL)	116 (26-641)*	150.2±114.3	129.8±70.7
HDL (mg/dL)	37 (9.6-88)*	38.39±10.14	40.07±13.82

Continuous data is presented in mean±SD, categorical data was presented in proportion (n(%)); * = data distribution was not normal and presented as median (minimum-maximum); NA = not applicable

Table 2. Prevalence ratio of high MMP-9 level in subjects with and without hyperglycemia

MMP-9 level (ng/mL)	With hyperglycemia (n=34)	Without hyperglycemia (n=38)	Prevalence ratio	CI 95%	P value
High (>1014.25)	30 (41.6%)	22 (30.6%)	2.88	1.16–7.14	0.004
Low (≤1014.25)	4 (5.6%)	16 (22.2%)			

CI=confidence interval

consumption, low physical activity and low consumption of fibers.¹⁴ DeRosa et al.¹⁵ showed that those with dyslipidemia had significantly higher level of MMP-9 than healthy subjects.¹⁵ In Indonesia, a recent study has demonstrated that dyslipidemia and metabolic syndrome has emerged, especially in urban area.¹⁶ Therefore, it is expected that dyslipidemic patients will be frequently encountered in acute coronary syndrome patients since dyslipidemia is one of the most important risk factors for coronary heart disease. The proportion of dyslipidemia in our study was relatively high, i.e. 65%; however, there was no significant difference between patients with and without hyperglycemia.

Obesity may affect MMP-9 levels. DeRosa et al.¹⁷ showed that MMP-9 levels in obese patients were significantly higher than in the control group ($p < 0.0001$).¹⁷ In our study, the mean body mass index between subjects with hyperglycemia and without hyperglycemia was comparable. Based on body mass index, the proportion of obese patients in our study was small. Furthermore, increased MMP-9 levels has also been identified in patients with hypertension, which reflects the magnitude of deposition and retention of type I collagen and other extracellular matrix in vascular wall leading to increased vascular tone.¹⁸ The proportion of hypertension in our study was quite high, i.e. 61%, which was comparable between patients with and without hyperglycemia. Taken together, obesity and hypertension in our study were not responsible for the different levels of MMP-9 observed among subjects with varied glucose levels.

Several previous studies have shown elevated MMP-9 levels in patients with type-2 diabetes mellitus.¹⁹⁻²¹ However, other studies indicated the opposite.^{11,22} The conflicting results

imply the complexity of glucose toxicity and insulin resistance in affecting MMP-9 turnover especially in chronic condition. In our study, the proportion of diabetes mellitus in all subjects was rather low, i.e. 26%. The majority of diabetic patients had increased blood glucose levels with a comorbidity of acute coronary syndrome (17 out of 19 patients).

In subjects with hyperglycemia, diabetic patients account for half of the patients. This chronic hyperglycemic state may have a contribution in increased MMP-9 levels among patients with hyperglycemia. MMP system in the vascular wall is activated in chronic hyperglycemia.⁸ Lewandowski et al.¹¹ has provided evidences that in patients with type-2 diabetes mellitus, circulating MMP-9 levels were more affected by chronic hyperglycemic condition rather than by acute hyperglycemia.¹¹ They showed the linear correlation between HbA1c and MMP-9 levels.¹¹ Another experimental study has also demonstrated increased MMP-9 activity in endothelial cells under chronic hyperglycemia environments as compared with cells under acute hyperglycemia (24 hours).¹⁹ In addition to chronic state, acute hyperglycemia might have also contributed to increased MMP-9 levels since half of the patients had no history of diabetes.

Several factors may affect MMP-9 levels in type-2 diabetes mellitus, such as consumption of statins, fibrates, ACE inhibitors, angiotensin receptor blockers, calcium channel blockers and acetyl salicylic acid.²³⁻²⁵ Statins and fibrates are the most widely used drugs for the treatment of hyperlipidemia in diabetic patients. These drugs have antiinflammatory and antioxidant properties. They improve endothelial function and stabilize atherosclerotic plaque through modulation of extracellular matrix homeostasis and reduction of MMP concentration and activity.²³ Acetyl

salicylic acid blocks cyclooxygenase activity; therefore, reducing the synthesis of prostaglandin and controlling the activity of MMP.²⁶ The effects of such medications in our study was difficult to assess because there was a lack of data regarding previous drugs taken by the subjects. However, since the previous diseases were comparable between subjects with and without hyperglycemia, we assumed that the impact of the drugs, if any, on MMP-9 levels were also comparable.

Our study showed a relationship between MMP-9 levels and hyperglycemia occurring in acute coronary syndrome. Patients with hyperglycemia had a prevalence ratio of 2.88 for having high MMP-9 levels while suffering from acute coronary syndrome. High MMP-9 levels may mediate the detrimental effects of hyperglycemia in acute coronary syndrome. Acute hyperglycemia exacerbates oxidative stress and RAGE production with subsequent MMP overexpression in the vascular wall.¹⁰ Moreover, on-admission hyperglycemic state alone is also associated with worse outcomes in acute coronary syndromes.²⁷ In combination with increased MMP-9 levels, these patients may have additional risk and burden for developing adverse events during hospitalisation. Further research should be performed to investigate the impact of hyperglycemia and increased MMP-9 levels in acute coronary syndrome.

The limitations of our study were the small sample size in each group, the incomplete data regarding previous medications and the measurement of blood glucose levels which was only performed once on-admission. Further study to overcome the limitations should be done to validate our finding.

CONCLUSION

Serum MMP-9 levels is significantly higher in patients suffering from acute coronary syndrome with hyperglycemia compared to those without hyperglycemia.

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