Acta Cardiologia Indonesiana
Web page: jurnal.ugm.ac.id/v3/jaci
pISSN:2460-5700
eISSN:2579-4345

Correlation Between Dipeptidyl Peptidase-4 Activity With Endothelial Dysfunction And The Complexity Of Coronary Artery Lesion In Patients With Acute Myocardial Infarction

Sigit Pratama Iustitia Nasruddin[1*], Heru Sulastomo[1,2], Ahmad Yasa[1,2]

[1]Department of Cardiology and Vascular Medicine, Faculty of Medicine, Universitas Sebelas Maret, Surakarta, Indonesia
[2]Department of Cardiology and Vascular Medicine, Dr. Moewardi General Hospital, Surakarta, Indonesia

ARTICLE INFO

*Corresponding author
Sigit Pratama Iustitia Nasruddin

Email: cardiologyclassdoktersigit@gmail.com

Address:
Jalan Ir. Sutami No. 36A, Kentingan, Surakarta, 57126, Indonesia

Keywords:
dipeptidyl-peptidase-4; flow mediated dilatation; SYNTAX score I

Manuscript submitted: 30 March 2020
Revised and accepted: 30 September 2022

ABSTRACT

Background: Cardiovascular disease is the most cause of mortality and morbidity around the globe. Recent study shows that Dipeptidyl-peptidase-4 (DPP-4) play roles in regulating the inflammation and metabolism process, as well as involved in the development of endothelial dysfunction and atherosclerotic disease.

Objective: This study aims to find the correlation between the activity of DPP-4 with endothelial dysfunction measured by Flow Mediated Dilatation (FMD) and the complexity of coronary artery lesion assessed by SYNTAX score I in patients with acute myocardial infarction.

Methods: A cross-sectional study was conducted in December 2019 – January 2020 in patients with acute myocardial infarction admitted and hospitalized in Dr. Moewardi Hospital, including ST-Elevation Myocardial Infarction (STEMI) and Non-ST-Elevation Myocardial Infarction (NSTEMI). Blood drawing, FMD examination and Diagnostic Coronary Angiography were performed. In order to find the correlation between DPP-4 with FMD and SYNTAX score I, Product Moment Pearson correlation test was used in data with normal distribution, and Rank Spearman test in data with abnormal distribution. Multiple correlation statistic test was used to establish the correlation between DPP-4 and FMD with SYNTAX score I.

Results: Forty patients were involved in the current study (32 males, 8 females). Between DPP-4 and FMD was proved to have strong negative and significant correlation (r = -0,49; p = 0,001). DPP-4 and SYNTAX score I were positively strong and significantly correlated (r = 0,373; p = 0,019). The result of multiple correlation analysis using regression statistic analysis show DPP-4 and FMD together correlated to SYNTAX score I significantly (R = 0,556, p = 0,001).

Conclusions: DPP-4 activity was proved to be correlated with endothelial dysfunction measured by FMD and complexity coronary artery lesion assessed by SYNTAX score I in patients with acute myocardial infarction.

INTISARI

Latar Belakang: Penyakit kardiovaskular merupakan penyebab utama kematian dan kecacatan di dunia. Studi terbaru menunjukkan Dipeptidyl-peptidase-4 (DPP-4) berperan dalam pengaturan inflamasi dan metabolisme, serta terlibat dalam berkembangnya disfungsi endotel dan penyakit aterosklerotik.

Tujuan: Untuk mengetahui korelasi antara aktivitas DPP-4 dengan disfungsi endotel yang diukur dengan Flow Mediated Dilatation (FMD) dan kompleksitas lesi arteri koroner yang dinilai dengan skor SYNTAX I pada pasien infark miokard akut.

Metode: Penelitian ini merupakan penelitian potong lintang yang dilakukan pada bulan Desember 2019 – Januari 2020 terhadap pasien IMA yang datang ke Rumah Sakit Dr. Moewardi baik dengan elevasi segmen ST (IMA EST) maupun tanpa elevasi segmen ST (IMA non EST). Dilakukan pengambilan darah, pemeriksaan FMD dan Diagnostic Coronary Angiography (DCA). Untuk mengetahui korelasi antara DPP-4 dengan FMD dan skor SYNTAX I digunakan uji korelasi Product Moment Pearson jika distribusi data normal, jika distribusi data tidak normal digunakan analisis statistik Rank Spearman. Untuk membuktikan hubungan DPP-4 dan FMD secara bersama-sama terhadap skor SYNTAX I digunakan statistik korelasi ganda.

Hasil: Sebanyak 40 pasien diikutsertakan pada penelitian ini (32 laki-laki, 8 perempuan). DPP-4 dan FMD berkorelasi negatif kuat dan signifikan (r = -0,49; p = 0,001). DPP-4 dan skor SYNTAX I berkorelasi positif kuat dan signifikan (r = 0,373; p = 0,019). Hasil analisis korelasi ganda dengan bantuan analisis statistik regresi didapatkan DPP-4 dan FMD secara bersama-sama berhubungan dengan skor SYNTAX I secara bermakna (R= 0,556; p = 0,001).

Kesimpulan:Terdapat korelasi antara aktivitas DPP-4 dengan disfungsi endotel yang diukur dengan FMD dan kompleksitas lesi ateri koroner yang dinilai dengan skor SYNTAX I pada pasien infark miokard akut.

Introduction

Cardiovascular disease is the leading cause of death and disability in the world. More than 2200 people in America die every day, and 1 death occurs in 40 seconds[1]. Data released by the Indonesian Ministry of Health showed that cerebro-cardiovascular disease is the leading cause of death in Indonesia. The mortality rate has increased over the years, reaching almost 30% in 2004 compared to 1975 which was only 5%[2]. Data from Riskesdas 2013 revealed the prevalence of coronary heart disease (CHD) in Indonesia at 1.5%[3]. Patients data obtained in Dr. Moewardi Hospital, Surakarta in 2014-2018, showed 1680 patients with Acute Coronary Syndrome (ACS), as many as 909 patients (62.1%) Acute Myocardial Infarction with ST segment elevation (STEMI), 296 patients (20.4%) infarction myocardial without ST segment elevation (NSTEMI) and 256 patients (17.5%) Unstable Angina Pectoris (UAP). There were 228 patients (15.9%) who died while undergoing treatment in the hospital[4].

Although the pathogenesis of atherosclerosis is quite significantly known, the underlying mechanism is not fully understood. Recent studies have shown Dipeptidyl-peptidase-4 (DPP-4), play a role in the regulation of inflammation and metabolism, as well as being involved in the development of atherosclerotic disease. At present, there is increasing clinical and preclinical evidence showing that DPP-4 is involved in cardiovascular disease[5]. Increased DPP-4 activity is associated with an increased risk of atherosclerosis, CHD and heart failure[6]. DPP-4 levels also correlate with inflammatory processes of blood vessels and endothelial dysfunction[7].

DPP-4 is one of powerful serine peptidase which showing expressed broadly in mammalian tissue. DPP-4 is expressed in endothelial cells, endothelial progenitor cells (EPC), several important immune cells (e.g., natural killer cells, monocytes, lymphocytes, and dendritic cells) and inflammatory cells (e.g., macrophages) in pathological conditions. Because of its wide distribution, inhibition of DPP-4 is a promising approach in various medical fields, such as regulation of inflammation, recovery of hematopoiesis, immunomodulation, and also in the case of angiogenesis8. DPP-4 inhibitors have a protective effect on the heart, including atherosclerosis[5], and increased endothelial function[9].

Endothelial dysfunction is involved in the development of atherosclerosis, which precedes structural changes in blood vessels as a clinical manifestation of cardiovascular disease. The occurrence of endothelial dysfunction in coronary and peripheral vessels is an independent predictor of cardiovascular events[10,11]. Endothelial function can be assessed non-invasively using FMD. FMD is related to coronary artery endothelial function, and independently predicts cardiovascular disease outcome [12].

The Synergy score between percutaneous coronary intervention with taxus and cardiac surgery (SYNTAX) I has been developed as a comprehensive angiographic assessment tool for quantification of coronary lesions with respect to number, location, and complexity. The SYNTAX I score is a good predictor for assessing cardiovascular events, cardiac death and myocardial infarction[13,14].

Methods

This study was a cross-sectional analytic observational study. The subjects were STEMI and NSTEMI patients who underwent treatment at Intensive Cardiovascular Care Unit of RSUD Dr. Moewardi, Surakarta, Central Java. The samples were taken consecutively from December 2019 to January 2020.

The inclusion criteria in this study were: the patients with AMI (based on chest pain complaints accompanied by elevated cardiac enzyme with either ST-segment elevation or without ST-segment elevation, onset of chest pain ≤ 24 h, and willing to be the subjects of the study).

The exclusion criteria for this study were: patients with previous history of acute coronary syndrome or chronic heart failure, patients with chronic renal failure, liver cirrhosis, chronic inflammatory disease or malignancy, patients with acute infection or sepsis, patient undergo DPP-4 treatment, patient with ineligible FMR result for analysis, or patient who rejected to become sample.

The blood sampling for FMA and DCA test was performed when the patients entered the Emergency Department of Dr Moewardi Hospital. The blood samples were taken from the antecubital vein. The blood samples obtained were put into EDTA tube and then centrifuged to separate plasma and blood cells. Plasma put into Eppendorf tube and stored at -800C temperature. Other routine laboratory tests were also performed, and the blood sampling was done before treatment. Then, spectrophotometry examination is performed to count DPP-4 activity. FMD activity was analyzed with GE Vivid E95 echocardiography in 24-72 hours range after patient first treatment. Coronary angiography administered through patient treatment and scored with SYNTAX I score by one experienced expert.

The data obtained were analyzed statistically using SPSS 22.0 software. The continuous characteristic data were tested using Shapiro-Wilk. Interclass Correlation Coefficient (ICC) analysis was administered to analyze reproducibility between FMD and SYNTAX I score. To test correlation between DPP-4, FMD, and SYNTAX I score, a parametric correlation test using Product Moment Pearson was performed; if the requirements were not met, there would be done Rank Spearman test. To test correlation between DPP-4 and FMD toward skot SYNTAX I score, a multiple correlation test was done.

Result

As many as 40 patients get measured of three main variables that studied in this research, including DPP-4, FMD which represent endothelial dysfunction variable and SYNTAX I score which represent coronary artery lesion complexity variable. Complete description of characteristics variable of this research showed in the Table 1.

Intraclass Correlation Coefficient (ICC) analysis conducted randomly on 15 samples. The FMD examination showed an intraobserver result of 0.998 and interobserver 0.998 which mean FMD measurement in this research have good reproducibility. The examination of SYNTAX I scores showed intra-observer score 0.997 and inter-observer 0.998, which mean that the measurement of SYNTAX I scores in this study had high and good reproducibility.

Before we analyze the correlation of each characteristic variables with the main research variables (DPP-4, FMD and SYNTAX I scores) as shown in Table 2. Furthermore, the results of the correlation analysis between the characteristic variables with main research variables scores are descripted in Table 3.

Table 1. Description of demographic, risk factor, Clinical condition and therapy variable.

Parameter	Mean / n	Deviation Standard/ %
Demography		
Age	57,30 years	11,65 years
Sex:		
Male	32	80,00 %
Female	8	20,00 %
Risk Factors:		
Diabetes Mellitus	9	22,50 %
Hypertension	18	45,00 %
Dislipidemia	1	2,50 %
Smoker	21	52,50 %
Stroke	2	5,00 %
Menopause	15	37,50 %
Clinical Conditions :		
BMI	23,07 kg/m2	4,10 kg/m2
Onset	8,64 hours	6,53 hours
Killip Class:		
Killip Class I	21	52.50 %
Killip Class II – IV	19	47,50 %
AMI type:		
STEMI	29	72,50 %
NSTEMI	11	27,50 %
Infarct location:		
Anterior	16	40,00 %
Non Anterior	24	60,00 %
eGFR	80,04	26,84
Laboratorium Parameter		
Hemoglobin	13,30 g/dL	1,39 g/dL
Hematocryte	41,97 %	4,20 %
Leukocyte	12,67 (103/µL)	7,78 (103/µL)
Thrombocyte	269,02 (103/µL)	53,77 (103/µL)
Ureum	34,03 mg/dL	17,69 mg/dL
Creatinine	0,99 mg/dL	0,32 mg/dL
Neutrofil	76,37 %	12,30 %
Lhymphocyte	16,52 %	9,95 %
Random Blood Sugar	176,48 mg/dL	102,61 mg/dL
Fasting Blood Suga	100,70 mg/dL	42,76 mg/dL
2-hours-post-prandial Blood Sugar	130,95 mg/dL	54,56 mg/dL
Total Cholesterol	216,28 mg/dL	274,30 mg/dL
LDL	116,20 mg/dL	48,71 mg/dL
HDL	39,39 mg/dL	16,79 mg/dL
Triglyceride	148,30 mg/dL	74,37 mg/dL
Echocardiography Parameter		
LVEF	40,77 %	10,56 %
Therapy		
Fibrinolitic	20	50,00 %
ACEI/ARB	38	95,00 %
CCB	5	12,50 %
Nitrat	4	10,00 %
Statin	40	100 %

Based on the results of simple correlation analysis and partial correlation, relationships between variables are calculated with multiple correlation coefficients, overall, the results of correlation analysis can be concluded in Table 4.

Discussion

Simple correlation analysis result between DPP-4 with FMD showed significant correlation result with a negative correlation value (r = -0.507, p= 0.001). In the partial correlation analysis with regression analysis between DPP-

4 and FMD, a significant correlation is obtained with a negative correlation value (r = -0.495, p = 0.001). Similar to previous studies by Barchetta et al, an increase in DPP-4 activity was significantly associated with a decrease in FMD (r = -0.37, p = 0.012). DPP-4 can negatively impact endothelial function. Mechanism which increases DPP-4 activity level are correspond with systemic inflammation process and development of atherosclerotic plaque15. Dissolved DPP-4 induces the proliferation of vascular smooth muscle cells and leads to atherogenesis condition. The results of simple correlation analysis between DPP-4 and SYNTAX I score in this study showed a significant correlation with a positive correlation value (r = 0.348, p = 0.028). In the partial correlation analysis with regression analysis between DPP-4 and SYNTAX I score, the correlation was also significant with a positive correlation value (r = 0.373, p = 0.019). Increased DPP-4 activity is associated with an increased risk of atherosclerosis and CHD6. Research conducted by Yang et al reported that DPP-4 activity was an independent predictor of coronary heart disease [OR 1.56 (95% CI 1.19-1.73) p = <0.01]. Patients with coronary heart disease (CHD) have significant increase of DPP-4 compared with patients without coronary heart disease (10.9 ± 4.9 vs. 6.4 ± 3.1, ng/L, P< 0.01). DPP-4 activity was positively correlated with coronary stenosis (r = 0.24, p <0.05) and length of coronary lesions (r = 0.19, P <0.05) demonstrated by coronary angiography in patients with CHD16.

Table 2. DPP-4, FMD and S

Correlation between variables	Regression analysis	
	Correlation coefficient	Probability
Simple correlation:		
DPP-4 with FMD	rxy1 = -0,507	0,001**
DPP-4 with SYNTAX I score	rxy2 = 0,348	0,028*
FMD with SYNTAX I score	ry1y2 = -0,48'	0,001**
Partial correlation:		
DPP-4 with FMD, Fixed SYNTAX I score,	rxy1.y2 = -0,495	0,001**
DPP-4 with SYNTAX I score, fixed FMD.	rxy2.y1 = 0,373	0,019*
Multiple correlation (R):		
DPP-4 with FMD with SYNTAX I score	Ry2.xy1 = 0,556	0,001**

** Significant at 1 % significancy level
* Significant at 5 % significancy level

In this study, we also performed a multiple correlation analysis which showed that the level of DPP-4 and FMD together were significantly associated with the SYNTAX I score with 1% significance level (p <0.01) with multiple correlation coefficient of R = 0.556. It means that if the DPP-4 and FMD levels together change, it will cause a significant change in the SYNTAX I score.

Limitation

There were several limitations to this study. First, we use a cross-sectional design with a small sample size, so we can't conclude the correlation between DPP-4 and endothelial dysfunction measured by FMD and coronary artery complexity lesion which measured by SYNTAX I score. Further cohort design research is necessary with multivariate analysis to look get causality relation. Also, there is no examination of GLP-1 which have protective effect on blood vessels by acting on endothelial cells.

Conclusion

There is a correlation between DPP-4 activity and endothelial dysfunction as measured by FMD and the complexity of coronary artery lesions that was assessed by the SYNTAX I score in patients with acute myocardial infarction.

Disclosures and Ethics

The Authors declare that there is no conflict of interest.

References

1. Vasan RS, Benjamin EJ, Sullivan LM, et al. 2012. The Burden of Increasing Worldwide Cardiovascular Disease. In: Valentin RAW, Robert AO, and Philip PW (eds). Hurst's The Heart. 13th Edition. New York: The McGraw-Hill Companies. 1241-1267.
2. Dharma S, Juzar DA, Firdaus I, et al. 2012. Acute myocardial infarction system of care in the third world. Neth Heart J. 20(6): 254-259.
3. Kemenkes RI. 2013. Riset Kesehatan Dasar; RISKESDAS. Jakarta: Balitbang
4. Wasyanto T and Tridamayanti A. 2019. Blood urea nitrogen as a predictor of in-hospital mortality in acute coronary syndrome patients. Indonesian J of Med. 4(3): 241-251.
5. Duan L, Rao X, Xia C, et al. 2017. The regulatory role of DPP-4 in atherosclerotic disease. Cardiovasc Diabetol. 16: 1-8.
6. Li JW, Chen YD, Lie YQ, et al. 2017b. Plasma dipeptidyl-peptidase-4 activity is associated with left ventricular systolic function in patients with ST-segment elevation myocardial infarction. Sci Rep. 7(1): 1-8.
7. Alvarez E, Dobarro BP, Pateiro MG, et al. 2018. Impact of advanced glycation end products on endothelial function and their potential link to atherosclerosis. Intech open. 211-230.
8. Lei Y, Hu L, Yang G, et al. 2017. Dipeptidyl peptidase-IV inhibition for the treatment of cardiovascular disease—recent insights focusing on angiogenesis and neovascularization. Circ J. 81(6):770–776.
9. Nunes JPI, Rodrigues JD and Melao F. 2014. Acute myocardial infarction associated to DPP-4 inhibitors. Heart Lung Vessel. 6(3): 180-186.
10. Bonetti PO, Pumper GM, Higano ST, et al. 2004. Noninvasive identification of patients with early coronary atherosclerosis by assessment of digital reactive hyperemia. J Am Coll Cardiol. 44(11): 2137-2141
11. Widlansky ME, Gokce N, Keaney JF, et al. 2003. The clinical implications of endothelial dysfunction. J Am Coll Cardiol. 42(7): 1149-1160.
12. Thijssen DHJ, Bruno RM, Mil ACC, et al. 2019. Expert consensus and evidence based recommendations

for the assessment of flow-mediated dilation in humans. Eur Heart J. 1-14.
13. Choudhary S. 2017. Association of syntax score with short-term outcomes among acute ST-elevation myocardial infarction patients undergoing primary PCI. Indian Heart J Teach Ser. 69: S20-S23.
14. Girasis C, Garg S, Raber L, et al. 2011. SYNTAX score and clinical SYNTAX score as predictors of very long-term clinical outcomes in patients undergoing percutaneous coronary interventions: a substudy of SIRolimus-eluting stent compared with pacliTAXel-eluting stent for coronary revascularization (SIRTAX) trial. Eur Heart J. 32: 3115-3127.
15. Barchetta I, Ciccarelli G, Barone E, et al. 2019. Greater circulating DPP4 activity is associated with impaired flow-mediated dilatation in adults with type 2 diabetes melllitus. Nutr Metab Cardiovasc Dis. 29: 1087-1094.
16. Yang G, Li Y, Cui L, et al.2016. Increased plasma dipeptidyl peptidase-4 activities in patients with coronary artery disease. PLoS ONE. 11(9): 1-14.