ORIGINAL ARTICLE

Journal of the ASEAN Federation of Endocrine Societies

Association of Acute Hyperglycemia and Diabetes Mellitus with Platelet-derived Microparticle (PDMP) Levels During Acute Myocardial Infarction

Hana Anindya Indana,[1] Ira Puspitawati,[2] Dyah Samti Mayasari,[3,4] Anggoro Budi Hartopo[3]

[1]*School of Medicine, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada – Dr. Sardjito Hospital, Yogyakarta, Indonesia*
[2]*Department of Clinical Pathology and Laboratory Medicine, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada – Dr. Sardjito Hospital, Yogyakarta, Indonesia*
[3]*Department of Cardiology and Vascular Medicine, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada – Dr. Sardjito Hospital, Yogyakarta, Indonesia*
[4]*Universitas Gadjah Mada (UGM) Academic Hospital, Yogyakarta, Indonesia*

Abstract

Objectives. This research investigates whether there is an association between acute hyperglycemia and diabetes mellitus and the level of circulating platelet-derived microparticles (PDMPs) during an initial episode of acute myocardial infarction (AMI).

Methodology. This was a cross-sectional study involving hospitalized AMI patients. Demographic and clinical data were obtained from hospital records. Diabetes mellitus was defined by the history of the disease, anti-diabetes medication use and/ or level of HbA1C ≥6.5%. Levels of HbA1c, admission random and fasting blood glucose levels were measured. Flow-cytometry method was used to determine the levels of PDMPs from collected venous blood through tagging with CD-41 FITC and CD-62 PE markers and a threshold size of <1 μm. The number of circulating PDMPs was compared according to glucometabolic state, namely acute hyperglycemia (admission random glucose ≥200 mg/dL and fasting glucose ≥140 mg/dL) and diabetes mellitus. The comparative analysis between groups was conducted with Student T-test or Mann-Whitney test, where applicable.

Results. A total of 108 subjects were included and their data analyzed. The level of circulating PDMPs was significantly lower in subjects with admission random glucose ≥200 mg/dL as compared to those with below level [median (interquartile range (IQR)]: 2,710.0 (718.0-8,167.0) count/mL vs. 4,452.0 (2,128.5-14,499.8) count/mL, $p = 0.05$) and in subjects with fasting glucose ≥140 mg/dL as compared to those with below level (median (IQR): 2,382.0 (779.0-6,619.0) count/mL vs. 5,972.0 (2,345.7-14,781.3) count/mL, $p = 0.006$). The level of circulating PDMPs was also significantly lower in patients with diabetes mellitus as compared to those without (median (IQR): 2,655.0 (840.0-5,821.0) count/mL vs. 4,562.0 (2,128.5-15,055.8) count/mL; $p = 0.007$).

Conclusion. Acute hyperglycemia and diabetes mellitus are significantly associated with a lower circulating PDMP level during an initial AMI episode.

Key words: hyperglycemia; diabetes mellitus; cell-derived microparticles; acute myocardial infarction

INTRODUCTION

Cardiovascular diseases (CVD) contribute to the highest number of deaths internationally, amounting to around one-third of all causes of death. Among CVDs, roughly 7.4 million deaths are due to coronary artery disease (CAD), a disorder of the blood vessels supplying the myocardia. CAD is the most common cause of acute myocardial infarction (AMI), which is a cardiac emergency that arises when blood flow to the myocardia is blocked due to an occlusive plaque with subsequent thrombosis in the coronary arteries.[1] It causes the flow of oxygen-rich blood to diminish triggering a reduction in the oxygen supply to the myocardia which results in its injury and infarction.[1]

Diabetes mellitus and hyperglycemia are among the risk factors for CVD.[2] Hyperglycemia is encountered in up to 50% of patients with AMI, especially in ST-elevation acute myocardial infarction (STEMI).[3]

eISSN 2308-118x (Online)
Printed in the Philippines

Received: September 19, 2022. Accepted: January 2, 2023.
Published online first: July 30, 2023.
https://doi.org/10.15605/jafes.038.02.03

Corresponding author: Anggoro Budi Hartopo, MD (Internist-Cardiologist Consultant), MSc, PhD
Department of Cardiology and Vascular Medicine,
Faculty of Medicine, Public Health and Nursing,
Universitas Gadjah Mada – Dr. Sardjito Hospital, Yogyakarta, Indonesia
Jalan Farmako Sekip Utara, Yogyakarta 55281, Indonesia
E-mail: a_bhartopo@ugm.ac.id
ORCiD: https://orcid.org/0000-0002-6373-1033

Diabetes mellitus, a disease characterized by chronic hyperglycemia, is an important risk factor for AMI and exists in about 30% of AMIs.[3] Our previous studies showed that in patients with acute hyperglycemia and diabetes mellitus, higher levels of blood glucose during AMI episodes increased the incidence of adverse cardiovascular events.[4,5] One mechanism that may explain the poorer prognosis is the enhanced platelet activation and subsequent thrombus formation.[6]

Platelet-derived microparticles (PDMPs) play an important role in CVD, especially in atherosclerotic CVD. They are small vesicles formed from platelet plasma membranes and released during platelet activation or apoptosis through exosome exocytosis and budding of the plasma membrane.[7] Our previous studies indicated that PDMP amounts increased during AMI episodes and are associated with worse short and long-term outcomes.[8,9]

In patients with diabetes mellitus, the PDMPs increased significantly compared to the normal population.[10] Furthermore, in patients with diabetes with CVD, the PDMPs were multiplied, indicating platelet activation in this population.[11] During an AMI episode, more enhanced platelet activation and subsequent platelet-enriched thrombus formation among patients with diabetes mellitus may amplify the production of PDMPs. However, despite the abundant data on increased circulating PDMPs among diabetes mellitus and stable CVD, the impact of acute hyperglycemia and diabetes mellitus during AMI on circulating PDMPs release has not yet been investigated. Therefore, circulating PDMPs might be used as a biomarker to assess advanced intracoronary thrombosis in acute hyperglycemia and diabetes mellitus patients during an AMI episode.

This research investigates the association between acute hyperglycemia and diabetes mellitus and circulating PDMP levels during the initial episode of AMI.

METHODOLOGY

This research used a cross-sectional methodology with 108 patients enrolled in the study. The included patients had AMI, both ST and non-ST segment elevation myocardial infarction (STEMI and NSTEMI), who were admitted and underwent hospitalization in the Intensive Cardiac Care Unit of Dr. Sardjito Hospital, Yogyakarta from January 2017 to January 2019. The AMI diagnosis was based on three parameters: anginal pain, abnormal electrocardiogram findings and increased level of troponin-I. An initial episode of AMI was defined as within 24 hours of hospital admission.

Specifically, the inclusion criteria were: (1) Diagnosis of STEMI and NSTEMI; (2) Chest pain onset <24 hours; (3) Age between 35 and 75 years old; and (4) Fee of chronic comorbidities (chronic renal failure, congestive heart failure, and hepatic cirrhosis).

The exclusion criteria were: (1) Unmeasured or missing random and fasting blood glucose levels; (2) Unmeasured or missing HbA1c level;(3) Concurrent acute infection and sepsis; (4) Concurrent acute stroke; and (5) Co-existing malignancies.

Demographic and clinical data were obtained from hospital records and collected into case report forms. Diabetes mellitus was determined from the patients' history of the disease, medical history of anti-diabetes medication use and/ or level of HbA1C ≥6.5%. Other risk factors were defined accordingly. Within 24 hours of admission, venous blood samples were taken for laboratory examination. Hematology parameters of hemoglobin, leukocytes and platelets, including HbA1c, were examined with an automated hematocytometer based on the hospital standard (Sysmex XN1000®, Sysmex, Kobe, Japan). The examination of admission random glucose and fasting glucose levels employed the hexokinase method (Cobas 6000® analyzer, Roche Diagnostic, Mannheim, Germany). Other chemical examinations were performed with a chemical analyzer in our hospital laboratory.

As previously described, the level of circulating PDMPs was measured through flow-cytometry method (FACS Calibur, Becton Dickinson, Maryland, USA) within 24 hours of admission. The PDMPs were identified by tagging with CD-41 FITC (Biolegend, San Diego, USA) and CD-62 PE markers (Biolegend, San Diego, USA). The threshold size of <1 μm was defined and the amount was gated and calculated with the standard formula as described previously.[8]

Based on admission random glucose level, subjects were divided into acute hyperglycemia (admission random glucose level ≥200 mg/dL) and those without acute hyperglycemia (admission random glucose level <200 mg/dL). Based on fasting glucose level, subjects were divided into fasting hyperglycemia (fasting glucose level ≥140 mg/dL) and those without fasting hyperglycemia (fasting glucose level <140 mg/dL).

The subjects were also divided based on their history of diabetes mellitus. The calculation of sample size was based on the comparative study, namely the sample size formulae for comparing two independent groups (acute hyperglycemia and diabetes mellitus versus none of the conditions) with continuous variables (circulating PDMP levels) as previously described.[12] With the type one error of 5% and type two error of 80%, each group's minimum sample size was computed at 45 subjects.

All subjects completed and signed an informed consent authorization to participate in this research. Universitas Gadjah Mada Medical and Health Research Ethics Committee and the Dr. Sardjito Hospital Institutional Review Board approved the research protocol with number: (KE/FK/720/EC/2016).

Statistical analysis

The comparison of numerical variables, including PDMP levels, between groups (with hyperglycemia versus without hyperglycemia and with diabetes mellitus versus without diabetes mellitus) was analyzed with Student T-tests or Mann-Whitney tests, where applicable, after normality distribution analysis with Kolmogorov-Smirnov test. The comparison of categorical variables utilized the Chi-square test or Fisher's exact test. The correlations between circulating PDMPs amounts and glucose levels as well as HbA1C were analyzed with Spearman's correlation test. The results with *p*-value <0.05 were considered significant. The statistical analysis was performed with the SPSS software version 25.0 (IBM Corp., Armonk, NY, U.S.A).

RESULTS

Subject characteristics

During the study period, 120 patients were admitted with AMI. Among these 120 patients, 108 subjects were eligible for analysis in this research, while 12 subjects were excluded due to lacking glucose or HbA1c data. Of the included AMI patients, 15 (13.9%) were NSTEMI and 93 (86.1%) were STEMI (Figure 1).

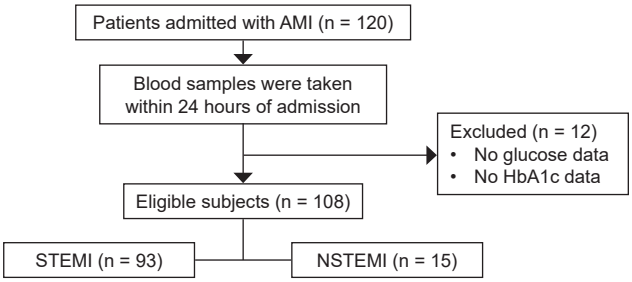

Figure 1. Study flowchart.

Admission blood glucose and circulating PDMPs amount

Patients with admission glucose level ≥200 mg/dL (n = 23, 21%) were observed to have a significantly higher percentage of diabetes mellitus (69.6%), STEMI diagnosis (100%), higher level of fasting glucose (mean: 187.8 ± 73.2 mg/dL) and higher concentration of HbA1c (mean: 9.1±2.3%), as compared to subjects with admission glucose level <200 mg/dL (n = 85, 79%) (Table 1).

The circulating PDMP level was significantly lower in subjects with admission glucose level ≥200 mg/dL as compared to those with below level (median interquartile range (IQR): 2,710.0 (718.0-8,167.0) count/mL vs. 4,452.0 (2,128.5-14,499.8) count/mL, $p = 0.05$).

Fasting glucose and circulating PDMPs amount

Patients with fasting glucose level ≥140 mg/dL (n = 33, 31%) also had a significantly higher percentage of diabetes mellitus (69.7%), lower level of leukocyte counts (mean: 11.6 ± 2.9 x 10^3/mm^3), higher level of admission glucose (mean: 224.1 ± 81.2 mg/dL) and higher percentage of HbA1c (mean: 8.6 ± 2.3%) as compared to patients with fasting glucose level <140 mg/dL (n = 75, 69%) (Table 2).

The circulating levels of PDMP were significantly lower in patients with fasting glucose level ≥140 mg/dL as compared to those with below level (median (IQR): 2,382.0 (779.0-6,619.0) count/mL vs. 5,972.0 (2,345.7-1,4781.3) count/mL, $p = 0.006$).

Diabetes mellitus and circulating level of PDMP

Among the patients diagnosed with diabetes mellitus (n = 27, 25%) compared to those without, there were fewer

Table 1. The characteristics of subjects based on admission random glucose level cut-off value of 200 mg/dL

Characteristics	Admission glucose level <200 mg/dL (n = 85)	Admission glucose level ≥200 mg/dL (n = 23)	*p*
Age (years), mean ± SD	54.9 ± 8.4	55.4 ± 8.8	0.41
Males, n (%)	79 (92.9)	19 (82.6)	0.13*
Females, n (%)	6 (7.1)	4 (17.4)	0.13*
Hypertension, n (%)	42 (49.4)	11 (44.1)	0.15
Diabetes mellitus, n (%)	11 (12.9)	16 (69.6)	<0.001
Dyslipidemia, n (%)	21 (24.7)	5 (4.6)	0.77
Ischemic heart disease, n (%)	24 (28.2)	6 (26.1)	0.84
Current smoker, n (%)	52 (61.2)	8 (34.8)	0.11
Bodyweight (kg), mean ± SD	65.5 ± 12.9	64.2 ± 12.0	0.33
Body mass index (kg/m^2), mean ± SD	26.5 ± 19.1	24.5 ± 3.1	0.31
STEMI, n (%)	70 (82.4)	23 (100.0)	0.02*
NSTEMI, n (%)	15 (17.6)	0 (0)	0.02*
Hemoglobin (g/dL), mean ± SD	13.8 ± 1.6	14.2 ± 1.7	0.11
Leukocytes (x10^3/mm^3), mean ± SD	12.9 ± 3.6	12.4 ± 3.4	0.24
Platelets (x10^3/mm^3), mean ± SD	265.6 ± 78.8	277.4 ± 89.7	0.27
HbA1c (%),* mean ± SD	6.1 ± 1.1 (n = 78)	9.1 ± 2.3 (n = 20)	<0.001
Fasting blood glucose (mg/dL), mean ± SD	117.1 ± 27.2	187.8 ± 73.2	<0.001
Urea nitrogen (mg/dL), mean ± SD	15.4 ± 7.5	16.8 ± 5.8	0.21
Creatinine (mg/dL), mean ± SD	1.2 ± 0.4	1.2 ± 0.4	0.48
PDMPs (count/uL), median (IQR)	4,452.0 (2128.5-14,499.8)	2,710.0 (718.0-8,167.0)	0.05

STEMI: ST-segment elevation acute myocardial infarction; NSTEMI: non-ST-segment elevation acute myocardial infarction; HbA1C: glycated hemoglobin; PDMPs: platelet-derived microparticles; SD: standard deviation; IQR: interquartile range. *Fisher-exact test.

males (77.8% versus 95.1%); lower percentage of current smokers (37% versus 61.7%);higher mean level of admission glucose (231.7 ± 76.9 mg/dL versus 138.7 ± 50.1 mg/dL); higher mean level of fasting glucose (187.1 ± 56.1 mg/dL versus 113 ± 31.6 mg/dL) and higher HbA1c percentages (8.6 ± 2.2% versus 6.1 ± 1.3%). (Table 3).

The circulating level of PDMP was significantly lower in patients with diabetes mellitus as compared to those without diabetes mellitus (median (IQR): 2,655.0 (840.0-5,821.0) count/mL vs. 4,562.0 (2,128.5-15,055.8) count/mL; $p = 0.007$).

Correlation between blood glucose and HbA1c levels and circulating PDMPs amount

The correlation test indicated that circulating level of PDMPs had a significantly negative correlation with fasting blood glucose (r = -0.213; $p = 0.03$). However, no significant correlations were found with admission blood glucose (r = -0.141; $p = 0.15$) and concentration of HbA1c (r = -0.059; $p = 0.57$), as shown in Table 4.

DISCUSSION

The research findings indicate that patients with acute hyperglycemia during AMI, defined by admission random blood glucose ≥200 mg/dL and fasting blood glucose ≥140 mg/dL, had lower levels of circulating PDMP. Furthermore, patients with a chronic hyperglycemia state, as in diabetes mellitus, were noted to have lower levels of circulating PDMP measured during the AMI episode. A negative correlation was found between glycemic indices and circulating PDMP levels, with significant findings only for fasting blood glucose levels.

Based on our study, patients with acute hyperglycemia had lower levels of circulating PDMP in comparison to those without acute hyperglycemia. Furthermore, during the fasting state, those with persistent acute hyperglycemia had significantly lower levels of circulating PDMP, when measured during the acute phase of AMI.

In previous studies, patients with diabetes mellitus had higher circulating PDMP than subjects without diabetes mellitus because there is an enhanced endothelial dysfunction and platelet hyperactivity in diabetes mellitus.[13] Plasma circulating PDMPs had significant and positive correlations with both fasting blood glucose and HbA1c levels.[14] Among patients with diabetes mellitus, significantly elevated levels of PDMPs were found also in patients with microvascular and macrovascular complications and associated with the severity of microvascular complications.[15,16] In the long term, PDMPs participate in atherosclerosis formation and progression by upregulating cytokines and intercellular adhesion molecular-1, facilitating leukocyte migration and hampering nitric oxide (NO) production.[17]

In a meta-analysis, diabetes mellitus was significantly associated with increased levels of PDMPs.[10] However, these previous findings were investigated in diabetes mellitus without an acute thrombosis event, such as AMI. In our study, which was comprised of subjects with AMI, the subjects with diabetes mellitus did not have a significant increase in PDMP levels. In contrast to previous findings, these patients had lower levels as compared to those without diabetes.

During AMI, PDMP levels increase especially at the beginning of the disease.[18] The increasing level of PDMPs was significantly associated with platelet activation, a vicious cycle of inflammation and thrombosis, the ischemic burden of myocardia and worsened clinical outcomes.[10,14,18]

In this current research, the circulating PDMPs were reduced in acute hyperglycemia and diabetes mellitus

Table 2. The characteristics of subjects based on fasting glucose level cut-off value of 140 mg/dL

Characteristics	Fasting glucose level <140 mg/dL (n = 75)	Fasting glucose level ≥140 mg/dL (n = 33)	*P*
Age (years), mean ± SD	54.6 ± 8.8	56.1 ± 7.5	0.20
Males, n (%)	71 (94.7)	27 (81.8)	0.04*
Females, n (%)	4 (5.3)	6 (18.2)	0.04*
Hypertension, n (%)	35 (46.7)	18 (53.0)	0.29
Diabetes mellitus, n (%)	4 (5.3)	23 (69.7)	<0.001
Dyslipidemia, n (%)	17 (22.7)	9 (27.3)	0.61
Ischemic heart disease, n (%)	18 (24.0)	12 (36.4)	0.19
Current smoker, n (%)	47 (62.7)	13 (39.4)	0.17
Bodyweight (kg), mean ± SD	64.7 ± 12.7	66.4 ± 12.8	0.26
Body mass index (kg/m^2), mean ± SD	24.1 ± 4.2	25.2 ± 3.2	0.11
STEMI, n (%)	67 (89.3)	26 (78.8)	0.14
NSTEMI, n (%)	8 (10.7)	7 (21.2)	0.14
Hemoglobin (g/dL), mean ± SD	13.8 ± 1.6	13.9 ± 1.7	0.45
Leukocytes (x10^3/mm^3), mean ± SD	13.4 ± 3.7	11.6 ± 2.9	0.01
Platelets (x10^3/mm^3), mean ± SD	272.6 ± 87.5	257.8 ± 66.9	0.19
HbA1c (%)*, mean ± SD	6.0 ± 0.8 (n = 70)	8.6 ± 2.3 (n = 28)	<0.001
Admission blood glucose (mg/dL), mean ± SD	134.7 ± 42.8	224.1 ± 81.2	<0.001
Urea nitrogen (mg/dL), mean ± SD	15.3 ± 7.2	16.4 ± 7.4	0.25
Creatinine (mg/dL), mean ± SD	1.3 ± 0.5	1.1 ± 0.4	0.08
PDMPs (count/uL), median (IQR)	5,972.0 (2,345.7-14,781.3)	2,382.0 (779.0-6,619.0)	0.006

STEMI: ST-segment elevation acute myocardial infarction; NSTEMI: non ST-segment elevation acute myocardial infarction; HbA1C: glycated hemoglobin; PDMPs: platelet-derived microparticles; SD: standard deviation; IQR: interquartile range. *Fisher exact test

Table 3. The characteristics of subjects based on presence of diabetes mellitus

Characteristics	Diabetes mellitus (n = 27)	Non-diabetes mellitus (n = 81)	*p*
Age (years), mean ± SD	56.0 ± 6.9	54.7 ± 8.9	0.25
Males, n (%)	21 (77.8)	77 (95.1)	0.02*
Females, n (%)	6 (22.2)	4 (4.9)	0.02*
Hypertension, n (%)	17 (63.0)	36 (44.4)	0.09
Dyslipidemia, n (%)	8 (29.6)	18 (22.2)	0.44
Ischemic heart disease, n (%)	11 (40.7)	19 (23.5)	0.08
Current smoker, n (%)	10 (37.0)	50 (61.7)	0.03
Bodyweight (kg), mean ± SD	64.7 ± 13.5	65.4 ± 12.5	0.40
Body mass index (kg/m^2), mean ± SD	24.8 ± 3.7	24.3 ± 4.0	0.32
STEMI, n (%)	22 (81.5)	71 (87.7)	0.42
NSTEMI, n (%)	5 (18.5)	10 (12.3)	0.42
Hemoglobin (g/dL), mean ± SD	13.6 ± 1.7	13.9 ± 1.6	0.17
Leukocytes (x10^3/mm^3), mean ± SD	12.0 ± 2.9	13.1 ± 3.7	0.09
Platelets (x10^3/mm^3), mean ± SD	262.6 ± 67.2	269.9 ± 85.3	0.34
HbA1c (%), mean ± SD	8.6 ± 2.2 (n = 24)	6.1 ± 1.3 (n = 74)	<0.001
Admission blood glucose (mg/dL), mean ± SD	231.7 ± 76.9	138.7 ± 50.1	<0.001
Fasting blood glucose (mg/dL), mean ± SD	187.1 ± 56.1	113.8 ± 31.6	<0.001
Urea nitrogen (mg/dL), mean ± SD	19.4 ± 7.6	14.4 ± 6.7	<0.001
Creatinine (mg/dL), mean ± SD	1.3 ± 0.4	1.2 ± 0.4	0.237
PDMPs (count/uL), median (IQR)	2,655.0 (840.0-5,821.0)	4,562.0 (2,128.5-15,055.8)	0.007

STEMI: ST-segment elevation acute myocardial infarction; NSTEMI: non-ST-segment elevation acute myocardial infarction; HbA1C: glycated hemoglobin; PDMPs: platelet-derived microparticles; SD: standard deviation; IQR: interquartile range. *Fisher exact test

Table 4. Correlation analysis between PDMP level with other variables

Variables	Coefficient correlation	
Age (years), mean ± SD	-0.090	0.36
Bodyweight (kg), mean ± SD	-0.036	0.72
Body mass index (kg/m^2), mean ± SD	-0.087	0.38
Hemoglobin (g/dL), mean ± SD	0.006	0.95
Leukocytes (x10^3/mm^3), mean ± SD	0.144	0.14
Platelets (x10^3/mm^3), mean ± SD	0.177	0.07
Admission blood glucose (mg/dL), mean ± SD	-0.141	0.15
Fasting blood glucose (mg/dL), mean ± SD	-0.213	0.03
HbA1c (%), mean ± SD	-0.059	0.57
Urea nitrogen (mg/dL), mean ± SD	-0.109	0.27
Creatinine (mg/dL), mean ± SD	0.037	0.71

HbA1C: glycated hemoglobin; PDMPs: platelet-derived microparticles; SD: standard deviation

during the initial phase of AMI during which intracoronary thrombosis was ongoing. Previous in-vivo and human studies showed that the growing intracoronary thrombi in AMI utilize PDMPs in culprit sites as adhesion and activation markers, which cause reduced amounts in the circulation or peripheral blood.[19] We suggest that in acute hyperglycemia and diabetes mellitus, more PDMPs are generated and function in the culprit sites rather than circulate in the blood. This may possibly explain the findings generated by this research, that there is a reduction of circulating PDMPs among acute hyperglycemia and diabetic subjects during an acute coronary event.

Reduced PDMPs because of platelet reactivity induced by antiplatelet medications has been reported. The loading dose and continuation of double antiplatelet treatment in AMI contribute to the reduction of PDMPs in circulation.[20,21] Our patients underwent a loading dose of double anti-platelets, which may have affected the level of PDMPs during the acute phase of AMI in both groups.

Our previous study indicated the persistence of PDMPs 30 days after the acute phase of AMI.[9] Another study indicated that microparticles derived from endothelial cells (EDMPs) did not significantly differ between patients with diabetes mellitus who suffered from acute coronary syndrome and those with stable CAD, which indicated that the release of apoptosis-induced EDMPs is increased in diabetes, irrespective of the chronicity of the coronary disease.[22]

The findings of our study suggest that circulating PDMPs may be a potential biomarker for enhanced thrombus formation in AMI among patients with diabetes mellitus and acute hyperglycemia. The reduced circulating PDMPs in the initial phase of AMI reflect exaggerated utilization in the culprit lesion. Therefore, it signifies the need for aggressive management in AMI subjects with diabetes mellitus and acute hyperglycemia such as coronary revascularization, adequate fibrinolysis, adequate antiplatelets and potential use of anticoagulants.

CONCLUSION

Patients with acute hyperglycemia and diabetes mellitus tend to have lower levels of circulating PDMP during an initial episode of AMI. The fasting glucose level was negatively correlated with the level of circulating PDMPs. However, a limitation of this study is the relatively small sample size which warrants further investigation with a larger sample size to verify the results.

Acknowledgments

The contribution of these people to the publication of this manuscript was worthy of acknowledgement: Teguh Triyono MD and Farid Abdullah (for FACS analysis), Erlinda Pretty Laksneri MD, Adysti Dhian R.P. MD, Ahmad Musthafa MD, Andro Diasmada MD, Gagah Buana Putra MD, Dwi Krisnawati MD, and Setiawan Widodo MD (for clinical data collection). This study is a final assignment for the Undergraduate Program

of Medicine Universitas Gadjah Mada by HAI as the first author of this manuscript.

Statement of Authorship
The authors certified fulfillment of ICMJE authorship criteria.

CRediT Author Statement
HAI: Conceptualization, Methodology, Validation, Formal Analysis, Investigation, Data Curation, Writing – original draft preparation, Visualization; **IP:** Methodology, Validation, Writing – review and editing; **DSM:** Methodology, Validation, Writing – review and editing, Supervision; **ABH:** Conceptualization, Methodology, Software, Formal Analysis, Investigation, Resources, Writing – review and editing, Supervision, Project administration, Funding acquisition.

Author Disclosure
The authors declared no conflict of interest.

Funding Sources
The research was funded by the following: (1) Penelitian Fundamental (1047/ UN1–P.III/LT/DIT-LIT/2016) from Universitas Gadjah Mada; (2) Penelitian Dana Masyarakat (Post-Doctoral Scheme) F.Y. 2017 from the Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada; and (3) Rekognisi Tugas Akhir Scheme F.Y. 2019 (3126/UN1/DITLIT/DIT-LIT/LT/2019) from Universitas Gadjah Mada. All funding was granted to ABH as a principal investigator.

References
1. Anderson JL, Morrow DA. Acute myocardial infarction. N Engl J Med. 2017; 25;376(21):2053-64. PMID: 28538121. https://doi.org/10.1056/NEJMra1606915.
2. Roth GA, Mensah GA, Johnson CO, et al. Global burden of cardiovascular diseases and risk factors, 1990-2019: Update from the GBD 2019 Study. J Am Coll Cardiol. 2020;76(25):2982-3021. PMID: 33309175. PMCID: PMC7755038. https://doi.org/10.1016/j.jacc.2020.11.010.
3. Milazzo V, Cosentino N, Genovese S, et al. Diabetes mellitus and acute myocardial infarction: Impact on short and long-term mortality. Adv Exp Med Biol. 2021;1307:153-69. PMID: 32020518. https://doi.org/10.1007/5584_2020_481.
4. Hartopo AB, Setianto BY, Gharini PP, Dinarti LK. On arrival high blood glucose level is associated with detrimental and fatal hospitalization outcomes for acute coronary syndrome. Cardiol Res. 2011;2(4):160-67. PMID: 28352385. PMCID: PMC5358223. https://doi.org/10.4021/cr56w.
5. Hartopo AB, Susanti VA, Anggraeni VY. The significance of glycated haemoglobin, randomized admission blood glucose, and fasting blood glucose on in-hospital adverse cardiac events in patients with ST-elevation acute myocardial infarction. J Med Sci. 2022;54(1):28-39. https://journal.ugm.ac.id/bik/article/download/68472/33722.
6. Undas A, Wiek I, Stêpien E, Zmudka K, Tracz W. Hyperglycemia is associated with enhanced thrombin formation, platelet activation, and fibrin clot resistance to lysis in patients with acute coronary syndrome. Diabetes Care. 2008;31(8):1590-5. PMID: 18487475. PMCID: PMC2494657. https://doi.org/10.2337/dc08-0282.
7. Wang ZT, Wang Z, Hu YW. Possible roles of platelet-derived microparticles in atherosclerosis. Atherosclerosis. 2016;248:10-6. PMID: 26978582. https://doi.org/10.1016/j.atherosclerosis.2016.03.004.
8. Hartopo AB, Puspitawati I, Gharini PP, Setianto BY. Platelet microparticle number is associated with the extent of myocardial damage in acute myocardial infarction. Arch Med Sci. 2016;12(3):529-37. PMID: 27279844. PMCID: PMC4889687. https://doi.org/10.5114/aoms.2016.59926.
9. Hartopo AB, Mayasari DS, Puspitawati I, Mumpuni H. Circulating platelet-derived microparticles associated with postdischarge major adverse cardiac events in ST-elevation acute myocardial infarction. Cardiol Res Pract. 2020;2020:6721584.
10. Li S, Wei J, Zhang C, et al. Cell-derived microparticles in patients with type 2 diabetes mellitus: A systematic review and meta-analysis. Cell Physiol Biochem. 2016;39(6):2439-50. PMID: 27832642. https://doi.org/10.1159/000452512.
11. Sun XD, Han L, Lan HT, et al. Endothelial microparticle-associated protein disulfide isomerase increases platelet activation in diabetic coronary heart disease. Aging (Albany NY). 2021;13(14):18718-39. PMID: 34285139. PMCID: PMC8351716. https://doi.org/10.18632/aging.203316.
12. Jankovic SM. Sample size calculation for comparative trials. Int J Biomed Health. 2018;6(2):62-4.https://doi.org/10.5455/ijbh.2018.6.62-64. https://www.ejmanager.com/mnstemps/220/220-1607282227.pdf?t=1687495410.
13. Kaur R, Kaur M, Singh J. Endothelial dysfunction and platelet hyperactivity in type 2 diabetes mellitus: Molecular insights and therapeutic strategies. Cardiovasc Diabetol. 2018;17(1):121. PMID: 30170601. PMCID: PMC6117983. https://doi.org/10.1186/s12933-018-0763-3.
14. Gkaliagkousi E, Nikolaidou B, Gavriilaki E, et al. Increased erythrocyte- and platelet-derived microvesicles in newly diagnosed type 2 diabetes mellitus. Diabet Vasc Dis Res. 2019;16(5):458-65. PMID: 31046456. https://doi.org/10.1177/1479164119844691.
15. Tsimerman G, Roguin A, Bachar A, Melamed E, Brenner B, Aharon A. Involvement of microparticles in diabetic vascular complications. Thromb Haemost. 2011; 106(2): 310-21. PMID: 21713319. https://doi.org/10.1160/TH10-11-0712.
16. Santilli F, Marchisio M, Lanuti P, Boccatonda A, Miscia S, Davì G. Microparticles as new markers of cardiovascular risk in diabetes and beyond. Thromb Haemost. 2016;116(2):220-34. PMID: 27173919. https://doi.org/10.1160/TH16-03-0176.
17. Zaldivia MTK, McFadyen JD, Lim B, Wang X, Peter K. Platelet-derived microvesicles in cardiovascular diseases. Front Cardiovasc Med. 2017;4:74. PMID: 29209618. PMCID: PMC5702324. https://doi.org/10.3389/fcvm.2017.00074.
18. Stępień E, Stankiewicz E, Zalewski J, Godlewski J, Zmudka K, Wybrańska I. Number of microparticles generated during acute myocardial infarction and stable angina correlates with platelet activation. Arch Med Res. 2012;43(1):31-5. PMID: 22306248. https://doi.org/10.1016/j.arcmed.2012.01.006.
19. Suades R, Padró T, Vilahur G, et al. Growing thrombi release increased levels of CD235a(+) microparticles and decreased levels of activated platelet-derived microparticles. Validation in ST-elevation myocardial infarction patients. J Thromb Haemost. 2015;13(10):1776-86. PMID: 26239059. https://doi.org/10.1111/jth.13065.
20. Kafian S, Mobarrez F, Wallén H, Samad B. Association between platelet reactivity and circulating platelet-derived microvesicles in patients with acute coronary syndrome. Platelets. 2015;26(5):467-73. PMID: 25025694. https://doi.org/10.3109/09537104.2014.940304.
21. Chyrchel B, Drożdż A, Długosz D, Stępień EŁ, Surdacki A. Platelet reactivity and circulating platelet-derived microvesicles are differently affected by P2Y12 receptor antagonists. Int J Med Sci. 2019;16(2):264-75. PMID: 30745807. PMCID: PMC6367525. https://doi.org/10.7150/ijms.28580.
22. Marei I, Chidiac O, Thomas B, et al. Angiogenic content of microparticles in patients with diabetes and coronary artery disease predicts networks of endothelial dysfunction. Cardiovasc Diabetol. 2022;21(1):17. PMID: 35109843. PMCID: PMC8812242. https://doi.org/10.1186/s12933-022-01449-0.