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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

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ABSTRACT

In an ST-segment elevation acute myocardial infarction (STEMI), glucose metabolism undergoes disturbance secondary to acute myocardial injury, which affects the clinical outcome during the acute phase. Glucose metabolic disturbance indices are glycated haemoglobin, admission random glucose, and fasting glucose in blood circulation during STEMI. This is a retrospective cohort study, aimed to investigate whether glycated haemoglobin, admission random blood glucose, and fasting blood glucose levels are the risk factors for developing in-hospital adverse cardiac events in STEMI. The result showed that among the three glucose metabolic disturbance indices, fasting glucose was an independent predictor (adjusted OR: 1.010 (95% CI: 1.001-1.018) and the most accurate factor (AUC 64.9 %) for adverse cardiac events. Other glucose metabolic indices, namely random blood glucose and glycated haemoglobin, were associated with increased odds to develop adverse cardiac events but they did not independently predict adverse cardiac events. Therefore, fasting blood glucose was an independent predictor and the most accurate factor for adverse cardiac events in the acute event of STEMI.

ABSTRAK

Pada infark miokard akut dengan elevasi segmen ST (IMA-EST), metabolisme glukosa mengalami gangguan sekunder akibat cedera miokard akut, yang berpengaruh pada luaran klinis selama fase akut. Indeks gangguan gluco metabolik yaitu hemoglobin terglikasi, glukosa acak saat admisi dan glukosa puasa dalam sirkulasi darah selama periode STEMI. Penelitian ini adalah studi kohort retrospektif, bertujuan untuk menyelidiki apakah hemoglobin terglikasi, glukosa darah acak saat admisi dan kadar glukosa darah puasa merupakan faktor risiko kejadian luaran klinis jantung yang merugikan di rumah sakit pada STEMI. Hasil penelitian menunjukkan bahwa diantara ketiga indeks gangguan gluco metabolik, glukosa darah puasa merupakan prediktor independen (adjusted OR: 1,010 (95% CI: 1,001-1,018) dan faktor yang paling akurat (AUC 64,9%) untuk kejadian klinis jantung yang merugikan. Glukosa darah acak saat admisi dan hemoglobin terglikasi, dikaitkan dengan peningkatan peluang untuk kejadian klinis jantung yang merugikan tetapi tidak secara independen memprediksi kejadian jantung yang merugikan. Oleh karena itu, glukosa darah puasa merupakan prediktor independen dan faktor paling akurat untuk kejadian klinis jantung yang merugikan pada STEMI.

Keywords:
STEMI;
blood glucose;
glycated haemoglobin;
fasting glucose level

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INTRODUCTION

Acute myocardial infarction with ST-segment elevation (STEMI) is a disease due to transmural injury of myocardial cells because of the thrombus occlusion in the coronary artery. Among acute myocardial infarctions, 25% to 45% are STEMI.[1] The complication and mortality in STEMI are still high especially in patients with high-risk profiles.[2] Diabetes mellitus (DM), a chronic state of increased blood glucose level, is one of the high-risk profiles associated with complications and mortality in STEMI.[3] Our previous study indicated the detrimental impact of increased blood glucose levels in STEMI, especially in DM.[4]

The glucose metabolism undergoes several adjustments which produce a stress hyperglycemic state STEMI, associated with increased catecholamine levels secondary to acute myocardial injury.[5] During the acute phase of STEMI, continuous glucose metabolic disturbance is reflected by glycated haemoglobin, admission random glucose, and fasting glucose measured in blood circulation.[6] These biomarkers are functional as early markers of long-standing glucose metabolic disturbance, as opposed to stress hyperglycemia which is an acute phase associated with current acute myocardial infarction.[6]

The poorly-controlled long-standing glucose metabolic control, as reflected by glycated haemoglobin level, is associated with a risk of cardiovascular diseases.[7] Studies showed the relationship between admission blood glucose and the mortality rate after acute myocardial infarction.[8] This study acknowledged the involvement of glycated haemoglobin in this prognostication and as an earlier marker of unrecognized DM during acute events[8,9] Previous study also showed that elevated admission random blood glucose was associated with in-hospital fatal events during STEMI.[10] The importance of acute or chronic gluco metabolic control in STEMI has been extensively studied with various conclusions.

The association between fasting blood glucose in the early phase of STEMI and adverse cardiac events have been established.[3,11,12] These studies lead to the clinical trial to overcome the acute hyperglycemia by lowering it into a basal fasting state with intensified-insulin treatment by 24 h insulin–glucose infusion protocol.[12,13] Within 24 h blood glucose control, the target fasting glucose level is an important predictor of adverse cardiac events.[13] In this study, we aimed to investigate the role of glycated haemoglobin, admission of random blood glucose, and fasting blood glucose levels on the risk of developing in-hospital adverse cardiac events in patients hospitalized with STEMI.

MATERIALS AND METHODS

Study design and Subjects

The study design was a retrospective cohort study. The subjects were patients with STEMI who were hospitalized in the Intensive Cardiac Care Unit of Dr. Sardjito General Hospital, Yogyakarta, Indonesia. The subjects were enrolled consecutively from 2014 to 2018. The subject's data were retrieved from the case report form of the previous study.[14,15] The inclusion criteria were: (1) diagnosis of STEMI, (2) age between 30 and 75 years, (3) onset of anginal pain less than 24 h, and (4) the data of glucometabolic, namely admission random glucose, fasting glucose and glycated haemoglobin parameters were available. The exclusion criteria were: (1) history of chronic kidney disease stage V, chronic heart failure NYHA $\geq$ II, hepatic cirrhosis, and malignancy, (2) the comorbidities during acute phase: acute systemic infection or/and sepsis, and (3) revascularization procedure before reaching our hospital. All subjects

were given consent information. The study had been approved by the ethics committee of the Faculty of Medicine, Public Health, and Nursing Universitas Gadjah Mada-Dr. Sardjito General Hospital, Yogyakarta, Indonesia (No: KE/FK/817/EC.).

Laboratory examination

Subjects were admitted and followed up during hospitalization in the intensive cardiac care unit. All procedures and treatments received by subjects were in accordance with the attending physicians. The blood sample was withdrawn on admission from antecubital veins before the revascularization procedure was performed if indicated. The random blood glucose was measured from this admission blood sampling. The fasting blood sampling, for 6-8 h fasting, was withdrawn in the morning within 24 h of admission, for measurement of fasting blood glucose and glycated haemoglobin. The central hospital laboratory performed these parameters by standard laboratory practice.

Outcomes

The characteristics of subjects were recorded during intensive hospitalization. The subject's observation was performed during intensive hospitalization to identify the outcome. The outcome of this research was adverse cardiac events occurring during intensive hospitalization, namely the composite of death, acute heart failure, cardiogenic shock, reinfarction, and ventricular arrhythmia requiring resuscitation. Death was determined as death from the cardiac cause. Acute heart failure was the symptom and sign of breathlessness, fatigue, and congestion with the use of intravenous diuretics. Cardiogenic shock was systolic blood pressure <90 mmHg, the signs of low perfusion, and the use of vasopressor drugs. Reinfarction was the recurrence of chest pain, ST-segment elevation and, elevation of creatine kinase-MB/troponin-I after subjects subsided clinically. Ventricular arrhythmia was ventricular tachycardia/fibrillation episodes requiring cardiopulmonary resuscitation.[14] The outcomes were assessed by the attending cardiologists and recorded in a report form. Subjects who discharge from intensive care without any aforementioned events were classified as subjects without adverse cardiac events.

Statistics analysis

The continuous data were tested for normality distribution with the Kolmogorov-Smirnov test after logarithmic transformation as a standard normalization procedure. The parametric and non-parametric tests were used accordingly. The comparison between subjects with adverse cardiac events and those without was performed with Chi-square or Fisher-exact test for categorical data, and for continuous data, the comparison was performed with the Student t-test or Mann-Whitney U test. The receiver operator characteristics (ROC) curve was constructed to compare the accuracy of random blood glucose, fasting blood glucose, and glycated haemoglobin for predicting adverse cardiac events. The univariate and multivariable analyses were performed to establish the independent predictors of adverse cardiac events. A logistic regression test was performed for multivariable analysis by including co-variables from univariate analysis with $p < 0.250$. For comparison, a $p < 0.05$ was determined as statistical significance.

RESULT

The subjects enrolled for this research were 269, mostly male (84.8%) and, a mean age of 56.6 years old.

During observation, 55 subjects (20.4 %) had adverse cardiac events. The subjects with adverse cardiac events were significantly older (p <0.001) and had greater creatinine levels (p =0.011) as compared to subjects with no adverse cardiac events. The proportion of diabetes mellitus, and other risk factors, were comparable between groups. The revascularization procedures did not differ significantly between the groups. Significant increases in random blood glucose, fasting blood glucose, and glycated haemoglobin levels occurred in subjects with adverse cardiac events. TABLE 1 and TABLE 2 show the characteristics of all subjects and their comparison between subjects with adverse cardiac events and those with no adverse cardiac events.

TABLE 1. The characteristics of all subjects with STEMI

Characteristics	All subjects (n=269)
Male sex [n (%)]	228 (84.8)
Age [(years), mean±SD]	56.6±9.1
Hypertension, [n (%)]	146 (54.3)
Diabetes mellitus, [n (%)]	64 (23.8)
Ischemic heart disease [n (%)]	34 (12.6)
Current smoker [n (%)]	110 (40.9)
Dyslipidemia [n (%)]	35 (13.0)
Obesity [n (%)]	86 (32.0)
Haemoglobin [(g/mL), mean±SD]	14.0±1.8
Leukocytes [(x103/mL), mean±SD]	13.3±3.7
Platelet [(x106/mL), mean±SD]	263.9±79.6
Creatinine [(g/dL), mean±SD]	1.2±0.5
Onset of STEMI [n (%)]	7.9±7.4
Anterior STEMI [n (%)]	140 (52.0)
Primary PCI [n (%)]	108 (40.1)
Fibrinolysis [n (%)]	102 (37.9)
Random glucose [(g/mL), mean±SD]	182.5±98.6
Fasting glucose [(g/mL), mean±SD]	134.4±58.3
Glycated haemoglobin [(%), mean±SD]	6.8±2.3

SD: standard deviation; STEMI: ST-elevation acute myocardial infarction; PCI: percutaneous coronary intervention.

TABLE 2. The comparison of subjects with adverse cardiac events and those with no adverse cardiac events

Characteristics	Adverse cardiac events(n=55)	No adverse cardiac events(n=214)	p
Male sex [n (%)]	47 (85.5)	181 (84.6)	0.872
Age [(years), mean±SD]	60.0±8.5	55.7±9.1	0.001
Hypertension, [n (%)]	34 (61.8)	112 (52.3)	0.208
Diabetes mellitus, [n (%)]	14 (25.5)	50 (23.4)	0.745
Ischemic heart disease [n (%)]	4 (7.3)	30 (14.0)	0.130*
Current smoker [n (%)]	25 (45.5)	85 (39.7)	0.440
Dyslipidemia [n (%)]	6 (10.9)	29 (13.6)	0.603
Obesity [n (%)]	34 (65.4)	66.3)	0.897
Haemoglobin [(g/mL), mean±SD]	13.7±1.8	14.1±1.7	0.168
Leukocytes [(x103/mL), mean±SD]	13.9±4.4	13.1±3.5	0.215
Platelet [(x106/mL), mean±SD]	246.2±66.4	268.4±82.2	0.065
Creatinine [(g/dL), mean±SD]	1.4±0.6	1.2±0.4	0.011
Onset of STEMI [n (%)]	7.9±5.8	7.9±7.7	0.930
Anterior STEMI [n (%)]	31 (56.4)	109 (50.9)	0.371
Primary PCI [n (%)]	24 (43.6)	84 (39.3)	0.554
Fibrinolysis [n (%)]	17 (30.9)	85 (39.7)	0.230
Random glucose [(g/mL), mean±SD]	165.5 (125.5-252.5)	140.0 (119.2-195.8)	0.027**
Fasting glucose [(g/mL), mean±SD]	129.0 (110.5-175.8)	114.0 (96.0-136.5)	<0.001**
Glycated haemoglobin [(%), mean±SD]	6.2 (5.6-8.9)	5.8 (5.3-7.1)	0.020**

SD: standard deviation; STEMI: ST-elevation acute myocardial infarction; PCI: percutaneous coronary intervention ;IQR: interquartile range; * Fischer exact test; ** Mann Whitney test

TABLE 3 shows the type of adverse cardiac events that occurred during intensive hospital care. Acute heart failure was the most common adverse cardiac event (58.2%), followed by ventricular arrhythmia (14.5%) and cardiogenic shock (9.1%). The death occurred in 10.9% of subjects. The random glucose level was highest in subjects with cardiogenic shock. The fasting glucose level was also highest in subjects with cardiogenic shock. In all subjects with all types of adverse cardiac events, the fasting glucose levels were higher than in subjects with no adverse cardiac events. There were no significant differences in glycated haemoglobin among subjects of all types and no adverse cardiac events.

TABLE 3. The comparison of random glucose, fasting glucose, and glycated haemoglobin levels based on the type of adverse cardiac events

Type of adverse cardiac events (n=55)	Random glucose	Fasting glucose	Glycated haemoglobin
Death (n=6, 10.9%)	131.0 (118.0-399.5)	128.0 (89.5-348.0)	6.1 (4.6-12.3)
Acute heart failure (n=32, 58.2%)	160.0 (119.0-227.0)	128.0 (113.0-162.0)	6.2 (5.6-8.9)
Cardiogenic shock (n=5, 9.1%)	373.0 (205.5-436.0)	135.0 (108.5-247.5)	7.9 (5.7-11.2)
Ventricular tachycardia/ fibrillation (n=8, 14.5%)	133.0 (127.0-228.0)	129.0 (97.0-197.0)	6.2 (5.7-7.5)
No adverse cardiac events(n=211)	142.0 (120.0-200.0)	115.0 (98.0-139.0)	5.8 (5.3-7.1)
p	0.006*	0.005**	0.315

*One-way ANOVA, with post-hoc test significant for: acute heart failure vs. cardiogenic shock, cardiogenic shock vs. ventricular tachycardia/ fibrillation, cardiogenic shock vs. no adverse cardiac events; **One-way ANOVA, with post-hoc significance for: death vs. no adverse cardiac events, acute heart failure vs. no adverse cardiac events

The ROC curve is shown in FIGURE 1. It indicates that the area under the curve (AUC) of fasting glucose level was the highest (64.9 %), followed by the AUC of glycated haemoglobin (61.3 %) and AUC of random glucose level (58.0 %).

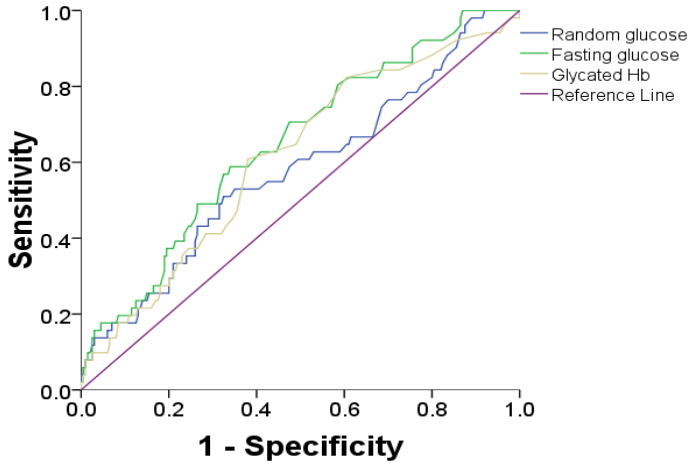

FIGURE 1. The receiver operator characteristics (ROC) curve to compare the area under the curve of random blood glucose, fasting blood glucose, and glycated haemoglobin in relation to adverse cardiac event

The univariate analysis shows that age, creatinine, random glucose, fasting glucose, and glycated haemoglobin levels were associated with increased odds to develop adverse cardiac events. The unadjusted OR of age was 1.058 (95% CI: 1.021-1.096), creatinine level was 2.501 (95% CI: 1.375-4.548), random glucose level was 1.003 (1.001-1.006), fasting glucose level was 1.008 (95% CI: 1.003-1.013) and glycated haemoglobin was 1.127 (95% CI: 1.001-1.270) (TABLE 4).

The multivariable analysis shows that age, creatinine level, and fasting glucose level were associated with increased odds to develop adverse cardiac events. The adjusted OR of age was 1.059 (95% CI: 1.019-1.100), creatinine level was 2.191 (95% CI: 1.188-4.041), and fasting glucose level was 1.010 (95% CI: 1.001-1.018) (TABLE 4).

TABLE 4. The univariate and multivariable analysis for parameters associated with adverse cardiac events

Co-variables	Univariate		Multivariable*	
	Unadjusted OR	95%CI	Adjusted OR**	95%CI
Age	1.058	1.021-1.096	1.059	1.019-1.100
Creatinine	2.501	1.375-4.548	2.191	1.188-4.041
Random glucose	1.003	1.001-1.006	1.000	0.995-1.006
Fasting glucose	1.008	1.003-1.013	1.010	1.001-1.018
Glycated haemoglobin	1.127	1.001-1.270	0.967	0.757-1.235

*Adjusted with age, hypertension, ischemic heart disease, haemoglobin level, leucocyte counts, platelet counts, creatinine level, random glucose level, fasting glucose level, and glycated haemoglobin; ** n = 251

TABLE 5. The changes and ratio of glucose level from admission to fasting state in all subjects

	All subjects (n=251)	Subjects with adverse cardiac events(n=51)	Subject with no adverse cardiac events(n=200)	p
Glucose reduction	30.0 (10.0-61.0)	27.0 (6.0-76.0)	31.0 (10.0-59.75)	0.789
Glucose ratio	1.26 (1.07-1.52)	1.22 (1.05-1.43)	1.28 (1.08-1.53)	0.318

The reduction of blood glucose level from admission to a fasting state was not significantly different between subjects with adverse cardiac events and those with no cardiac events. The glucose ratio, the value of random glucose:fasting glucose, also did not significantly differ (TABLE5).

DISCUSSION

Our current study inferred that among the three glucose metabolic disturbance indices, fasting glucose was an independent predictor and the most accurate factor for adverse cardiac events in the acute period of STEMI. Other glucose metabolic index measures, namely random blood glucose and glycated haemoglobin, were associated with increased odds to develop adverse cardiac events but they did not independently predict adverse cardiac events. Other independent predictors were age and creatinine level.

In the DIGAMI-2 trial, the intense hyperglycemia treatment initiated by insulin–glucose infusion throughout

the first 24 h with the target of normoglycemia after acute myocardial infarction was performed.[13] During the first 24 h, the insulin-glucose infusion was associated with a more reducing blood glucose level and increased incidence of hypoglycemia, while glycated haemoglobin level remained stable.[13] The insulin-initiated infusion was intended to rapidly achieve a normalized blood glucose level.[13] This study concluded that random blood glucose, along with glycated haemoglobin, was a significant and independent mortality predictor jointly with the other conventional risk factors, namely age, heart failure, and elevated serum creatinine.[13] This landmark study supports the suggestion that hyperglycemia is associated with increased adverse events, while normalization of glucose levels benefits patients.

Studies show that admission blood glucose and peak glycemia state are independent predictors for in-hospital mortality in STEMI patients.[16,17] The systematic review and meta-analysis demonstrated that on admission hyperglycemia had an increased risk of reperfusion failure in STEMI patients undergoing primary percutaneous coronary intervention, on those associated with worse adverse events.[18] Higher admission blood glucose level is also related to high burden thrombus and plaque erosion among STEMI.[19] Corroborated and contrasted these findings, our study showed that on admission random blood glucose was increased the risk of adverse cardiac events, however, its risk association was not independent.

Glycated haemoglobin did not significantly change during observation in the DIGAMI-2In DIGAMI-2 trial, but it was associated independently with mortality.[13] Not only in patients with diabetes mellitus, non-diabetic STEMI patients with high glycated haemoglobin levels had endothelial dysfunction and accelerated inflammatory response which is associated with adverse cardiac events following STEMI.[20] Glycated haemoglobin was independently associated with damaged left ventricle diastolic function and elevated filling pressures after STEMI.[21\] However, in a study that included a large number of consecutive STEMI patients with DM who underwent revascularization intervention, glycated haemoglobin was not associated with mortality in any the short or the long term after acute STEMI episodes.[22] Our current study indicated that glycated haemoglobin level was associated with increased odds to develop in hospital adverse cardiac events; however, it did not associate with adverse cardiac events independently.

There is a visit-to-visit fasting blood glucose variability which is proven as an independent predictor of left ventricular unfavorable remodeling in DM patients with STEMI.[23] Furthermore, the glycemic variability which measures the rising and descending acute glucose alteration independently associated with adverse cardiac events in STEMI patients.[24] Higher glycemic variability implicates increased oxidative stress, cytokine release, and endothelial dysfunction which unfavorably influences STEMI outcomes during acute care.[25] These glucose level fluctuations become potential therapeutic targets to reduce myocardial reperfusion injury in STEMI and its related adverse event.[25] Fasting blood glucose alone was independently associated with coronary microvascular obstruction after primary revascularization in STEMI patients without diabetes mellitus.[26] Furthermore, elevated fasting blood glucose level was independently associated with 30-day heart failure and left ventricular systolic dysfunction in patients undergoing primary PCI for STEMI but without diabetes mellitus.[27] Fasting blood glucose also correlated with increased left ventricular end-diastolic

pressure in STEMI patients which was further associated with worse clinical outcome.[28] Incidence of in-hospital adverse events significantly increases in STEMI patients if there are combined elevated random and fasting plasma glucose.[29] Both random and fasting glucose were independent predictors for in-hospital adverse cardiac events and they had good and similar predicting values of in-hospital adverse events.[29] Supporting these findings, in our current study, fasting blood glucose was an independent factor for developing in hospital adverse cardiac events. It surpassed other glucose metabolic index measures, namely random blood glucose and glycated haemoglobin.

This study had several limitations worth mentioning. First, the study design of the retrospective cohort study should be corroborated by a prospective cohort study. Second, the unicenter research should be replaced by including more centers in a multicenter study. Third, the subject number needs to be increased by including more subjects or more centers, and lastly, the follow-up period should be lengthened to detect the long-term consequences of glucose metabolic index disturbance in STEMI.

CONCLUSION

Fasting glucose level was an independent predictor and the most accurate risk factor for adverse cardiac events in the acute event of STEMI, as compared with other gluco metabolic index measures, namely random glucose level, and glycated haemoglobin. Other independent co-variables were age and creatinine level.

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