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The Predictive Value of Glucagon-Like Peptide 1 Plasma Levels on Acute Heart Failure

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ABSTRACT

Acute Heart Failure (AHF) is one of the mechanical complications of Acute Myocardial Infarct (AMI). The diagnostic approach of AHF caused by AMI is based on clinical score, imaging, use of invasive instruments, and laboratory parameters. Glucagon-Like Peptide-I (GLP-1) is an incretin hormone derivate of proglucagon gene transcription, secreted by the L cells from the mucosa of the ileum, colon, and rectum. The cardioprotective effect of GLP-1 through the dependent and independent pathway produces a direct and indirect cardiovascular effect that increases the functional capacity in AHF patients. This study aims to find the predictive value of plasma GLP-1 towards the incidence of AHF in patients with AMI. This study was conducted on 35 patients diagnosed with AMI at Dr. Moewardi General Hospital Surakarta, in October-December 2020. Glucagon-like peptide-I was measured using the ELISA sandwich. The cut-off of plasma GLP-1 was determined using the Receiver Operating Characteristic (ROC) curve. Statistical analysis showed an RR (95% CI) of 2.292 (0.587–8.943) with a p=0.229 for age, 1,143 (0.299–4.367) with a p – 0.127 for a history of type 2 diabetes (T2DM) and plasma GLP-1 concentrations below Cut-Off Value (COV), which was 2.881 (0.729–11.381) with p=0.127. Age, a history of T2DM, and plasma GLP-1 below COV did not significantly affect AHF complications in patients with AMI.

Keywords: Acute heart failure, acute myocardial infarct, glucagon-like peptide-1

INTRODUCTION

Acute Heart Failure (AHF) is one of the mechanical complications of Acute Myocardial Infarct (AMI). Benjamin *et al.* states that the burden of CVD therapy including AHF in AMI in the United States between 2014–2015 reached 356.2 billion dollars and is predicted to increase up to 749 billion dollars in 2035.[1-4] Acute heart failure patients in AMI need immediate diagnosis and therapy to minimalize the lost it can cause. Diagnostic approach of AHF in AMI is based on clinical scoring, imaging, use of invasive instruments and laboratory parameters, but each with their own weaknesses and strengths.[1,3]

Glucagon-like peptide-1 has a pleiotropic and metabolic effect such as insulin secretion stimulation, glucagon production blockade, natriuresis and diuresis increase. Glucagon-like peptide-1 is currently used as DM therapy alongside dipeptidyl peptidase-4 inhibitor (DPP-4i).[5,6] Other studies have shown the cardiovascular effects of GLP-1. Increased secretion of GLP-1 triggers a cardioprotective effect in the form of improvement of myocardial function and an increase in global and regional Left Ventricular Ejection Fraction (LVEF) in the post-infarct period through the dependent and independent pathway.[7-9] These findings show that GLP-1 concentrations can predict the occurrence of AHF in AMI patients, which is why this study's purpose is to determine the predictive value of plasma GLP-1 towards AHF in patients with AMI.

METHODS

This was an analytic observational study to determine the predictive value of plasma GLP-1 towards AHF in patients with AMI. This study was conducted in Dr. Moewardi General Hospital (RSDM) Surakarta during October–December 2020.

Study patients were chosen based on the following inclusion criteria: age of 18–72, a new AMI patient (fulfilling the STEMI and NSTEMI clinical criteria) with clinical presentation of chest pain < 24 hour. Exclusion criteria were a history of AMI or congestive heart failure, patients diagnosed with liver cirrhosis, chronic kidney failure, bowel disorders, malignancy or acute inflammation, patients with sepsis or severe infection, patients on vitagliptin and sitagliptin therapy (DPP-4i), incomplete medical records, patients with cardiac

intervention and pre analytic factors (lysed of icteric). Informed consent was requested before data was collected. Patients characteristics were obtained from anamnesis and physical examination, while lipid profile and GLP levels were from laboratory examinations.

Samples were retrieved once when the patient was admitted to the Emergency Room (ER). One tube (3 mL) of venous blood with EDTA anticoagulant was collected for each patient. Samples were centrifuged at 1000xg for 15 minutes to separate the plasma from blood components. Plasma was inserted into aliquots and stored at -80C. Glucagon-like peptide examinations used the ELISA sandwich method. ELISA kit microplates were coated with specific human GLP-1 antibodies. Samples or standards were added to the microplate wells, followed by specific antibodies for human GLP-1, and then conjugated avidin-Horse Radish Peroxide (HRP) was added in each well before they were incubated. The free components were thrown away by washing, then substrate was added to each well. Only wells with human GLP-1, biotinylated antibody and conjugated avidin-HRP produced a bluish color. The substrate-enzyme reaction was stopped by adding stopping solution and changed into yellow. Optical Density (OD) was measured with spectrophotometry at the wavelength of 450+2 nm. Optical density value portrayed the concentration of human GLP-1 in the sample. The detection length was 1.56–100 pg/mL and the analytical sensitivity was 0.94 pg/mL.

Categorical data were presented in frequency and percentage, while numerical data were presented as mean+Standard Deviation (SD). The receiver Operating Curve (ROC) was used to determine the cut-off of GLP-1 concentrations in AHF. The correlation between the independent variables (plasma GLP-1, age, and history of DM) with AHF in this study was analyzed using Chi-Square/Fisher exact test to find the Relative Risk (RR). Multivariate analysis was done if the $p < 0.25$ in the bivariate analysis to find the adjusted RR to see the role of plasma GLP-1 concentrations and other variables in effecting the occurrence of AHF in post-AMI patients. Analysis was done with a Confidence Interval (CI) 95% and $p < 0.05$ are deemed statistically significant. Statistical analysis was done with SPSS version 20.0 (IBM SPSS Statistics for Windows, 20.0 version Armonk, NY: IBM Corp).

This study was approved by the Health Research Ethics Commission Dr. Moewardi Hospital with number 1.173/X/HREC/2020.

RESULTS AND DISCUSSIONS

This study was conducted on 35 patients with new cases of AMI (either STEMI or NSTEMI) diagnosed by clinicians and undergoing care in the Intensive Cardiovascular Care Unit (ICVCU) and had laboratory examinations at the Clinical Pathology Installation of RSDM in Surakarta, Central Java during October–December 2020.

Table 1. Patients characteristics based on anamnesis and physical examination

Characteristics	n (%)	AHF		P
		Yes	No	
N	35	18 (51.43%)	17 (48.57%)	
Age[b] (years old)	57.11 ±13.34	61.06 ±9.86	52.94±15.46	0.071
Gender[a]				0.711
Male	26 (74.3%)	14 (53.8%)	12 (46.2%)	
Female	9 (25.7%)	4 (44.4%)	5 (55.6%)	
BMI[c] (%)	23.40 (15.62-32.04)	23.35 (15.62-29.80)	23.40 (19.53-32.04)	0.729
Hypertension[a]				0.060
Yes	19 (54.3%)	7 (36.84%)	12 (63.16%)	
No	16 (45.7%)	11 (68.75%)	5 (31.25%)	
Smoking history[a]				0.615
Yes	18 (51.4%)	10 (55.6%)	8 (44.4%)	
No	17 (48.6%)	8 (47.1%)	9 (52.9%)	
Glycemic control[a]				0.392
Poor	10 (28.6%)	4 (40.0%)	6 (60.0%)	
Good	25 (71.4%)	14 (56.0%)	11 (44.0%)	
Diagnosis[a]				0.129
STEMI	21 (60.0%)	13 (61.9%)	8 (38.1%)	
NSTEMI	14 (40.0%)	5 (35.7%)	9 (64.3%)	

Table 2. Lipid profile of the research patients

Characteristics	n (%)	AHF		P
		Yes	No	
Total cholesterol	169.63±52.23	159.94±32.82	179.88±66.59	0.277
HDL (mg/dL)	37.12±9.89	37.07±10.10	37.18±9.98	0.974
LDL (mg/dL)	114.40±42.83	106.22±30.78	123.06±52.32	0.251
Triglyceride (mg/dL)	121 (49-357)	105.50 (58-357)	139 (49-344)	0.520

a: Table explanation: a nominal data; frequency (%); Chi-Square/Fisher-exact test
b: normal distribution data (mean±SD), differential test with independent T-test; c: not normal distributed data [median (minimum–maximum)], differential test with Mann-Whitney U, *p<0.05 statistically significant; Hb: Hemoglobin; BMI: Body Mass Index; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; NLR: Neutrophil Lymphocyte Ratio; eGFR: estimated Glomerular Filtration Rate; HDL: High Density Lipoprotein; LDL: Low Density Lipoprotein; n: number (of patients); %: percentage; mmHg: millimeter of mercury; g/dL: gram per deciliter; mL/min/1.73 m^2: milliliter per minute per 1.75 cubic meter; mg/dL: milligram per deciliter

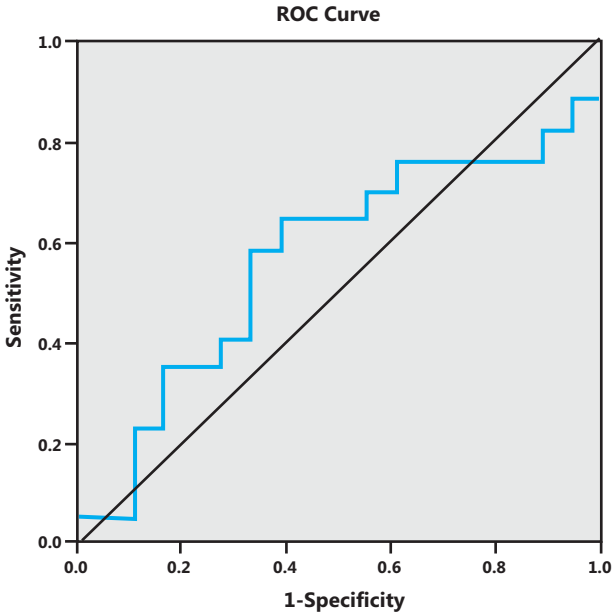

Figure 1. ROC curve of plasma GLP-1 levels according to AHF incidence

The characteristics data shows that there were 26 male patients (74.29%) and 9 female patients (25.71%). The proportion of male patients with the complication of AHF was higher than females (14 patients (79.3%) vs. 4 patients (20.7%)) but this finding was not statistically significant (Table 1). Body Mass Index (BMI) data shows that the group with AHF as a complication has a lower BMI [23.35 (15.62 0 29.8) kg/m2] compared to the group without AHF [23.4 (19.53–32.040 kg/m2], and in the overweight group, but this data had no statistically significant differences (Table 1).

History of hypertension (54.28%) and history of smoking (51.4%) were no statistically significant relation to AHF post-AMI (Table 1). The type of AMI in the patients was mostly STEMI for 21 patients (60%) and AHF in 13 patients (61.9%), which was higher than STEMI without AHF for only 8 patients (38.1%). Patients with NSTEMI were a total of 14 patients (40%) with AHF in 5 patients (35.7%), which was lower than those without AMI with a total of 9 patients (64.3%), but again, these results were not statistically significant.

Subject characteristics show that there was no significant difference between total cholesterol levels, HDL, LDL and triglyceride levels between the group with AHF as a complication and the group with no AHF (p=0.277; p=0.974; p=0.251; p=0.520). Dyslipidemia criteria data did not show significant differences between the group with AHF and the group without AHF (Table 2).

The cut-off value of plasma GLP-1 levels to predict AHF post-AMI is 20.135 pg/mL with an AUC of 0.569 and CI 95% (0.371–0.766). Determination of the cut-off value was taken from the highest sensitivity value with the highest specificity. The determination of HLP-1 concentration cut-off used a formula for the research variable categories. The results of plasma GLP-1 concentration show that from 35 patients there were 17 patients (48.6%) in the GLP-1 < 20.135 pg/mL category and 18 patients (51.4%) in the GLP-1> 20.135 pg/mL category (Figure 1).

Statistical analysis for the relationship between age, history of T2DM, and GLP-1 plasma concentration towards the occurrence of AHF showed an RR (95% CI) of 2.292 (0.587–8.943) for age with p+ 0.229, and RR (95% CI) of 1.143 (0.299–4.367) with p – 0.845 for a history of T2DM. The statistical analysis for GLP-1 plasma levels showed a tendency of lower GLP-1 levels in patients acquiring AHF compared to those without AHF but had an R (95% CI) of 2.881 (0.729–11.381) with a p=1.027. Age,

Table 3. The relationship between age, history of T2DM, and plasma GLP-1 concentration toward AHF

Variable	AHF		RR (95%CI)	P
	Yes (n=18)	No (n=17)		
Age[a]				
≥60 y.o.	10 (62.5%)	6 (37.5%)	2.292 (0.587-8.943)	0.229
<60 y.o.	8 (42.1%)	11 (57.9%)	Ref.	-
History of T2DM [a]				
Yes	8 (53.3%)	7 (46.7%)	1.143 (0.299-4.367)	0.845
No	10 (50.0%)	10 (50.0%)	Ref.	-
GLP-1(pg/mL)[a]				
<20.135	11 (64.7%)	6 (35.3%)	2.881 (0.729-11.381)	0.127
≥20.135	7 (38.9%)	11 (61.1%)	Ref.	-

Table description: a nominal categorical data; frequency (%); Chi-Square/Fisher- exact test.[b] Numeric data not normally distributed; median (min-max); Mann-Whitney test

history of T2DM, and GLP-1 plasma concentrations all showed non statistically significant results towards the occurrence of AHF complications in post-AMI patients (Table 3).

The results of this study show that GLP-1 plasma concentration cannot be a predictive value towards occurrence of AHF in patients with AMI. This study results are not in line with previous studies even though the patient characteristics are similar. Previous research showed that the male proportion was higher than the female, respectively 60%, and 70.7%.[10,2] Males are more likely to do physical activities and have a different lifestyle such as smoking and excessive alcohol drinking compared to females. Hormones also have a protective effect to the female cardiovascular system.

Body mass index results also did not show a significant impact on the occurrence of AHF. Insignificant results were also found by Rahayu, that concluded that BMI is a less specific anthropometric tool to grade obesity.[11] Results of Simonenko are in concordance with this study by explaining the Obesity paradox principle, where a higher BMI produces a better prognosis in patients with AHF, due to the theory that adipose tissue produces Tumor Necrosis Alpha (TNF-a) receptors that bind TNF-a resulting in a protective effect in AHF.[12]

The post-AMI patients of this study with a history of hypertension had lower AHF as complications compared with those without AHF (36.84% vs. 63.16%). A history of hypertension is more likely to cause AHF if the hypertension is prolonged and not controlled causing various structural changes in the myocardial, coronary vessels, and the hearts conduction system, further causing Left Ventricular Hypertrophy (LVH), Coronary Artery Disease (CAD), AMI and finally AHF.[12]

A history of smoking is a risk factor for AMI and other cardiovascular diseases, but the statistical analysis in this study showed statistically insignificant results (p=0.615) between the incidence of AHF post-AMI. Iskandar *et al.* showed similar results with p=0.270.[13] These conditions are due to other influencing factors, such as grade of smoking addiction (low, medium, high), duration, number and type of cigarette consumed, the length of smoking cessation, age, genetics, blood pressure, and alcohol consumption.[14]

Poor glycemic control is linked to higher risks of AHF in patients with or without T2DM. In patients with T2DM 1% increase of HbA1c causes an 8–36% increased risk of AHF.[15,16] in this study, the relationship between poor glycemic control and AHF was not significant (p=0.392). Insignificant results might be due to patients that usually end in AHF and death, having HbA1c levels > 9%, while the American Diabetes Association (ADA) has regulations for target therapy at HbA1c <7% to prevent poor glycemic control.[17,18]

The type of AMI did not have a significant effect on AHF with p=0.129. These results are in concordance with Taguchi *et al.* and Alhabib *et al.* stating that STEMI was higher than NSTEMI in HF post-AMI respectively 21.5% and 57%; and 23% and 43%, this condition is caused by an occlusion in one or more coronary artery in STEMI that causes AHF and requires emergency care.[2,19]

Lipid profile data also didn't show significant differences between the group with AHF complications and the group without AHF. These results are as in a study by Welling *et al.* with no significant difference between dyslipidemia criteria for those with AHF complications and no AHF (p=0.199).[13] Blecker *et al.* and Villanueva *et al.* state

other causes can be due to Single-Nucleotide Polymorphism (SNPs) genetic variations such as Proline/Serine-Rich Coiled-coil protein 1 (PSRC1) and cadherin EGF LAG seven-pass G-type receptor 2 (CELSR2).[20,21]

Statistical analysis between age and AHF show that age is not statistically significant in affecting AHF, which is estimated to be due to patients who are hospitalized are usually those aged 65 and above, while in this study, the mean age for AHF patients was 60.06 years old (SD+9.81), early diagnosis and proper therapy of AHF effects the AHF complications in this study.[18]

Statistical analysis of the history of T2DM and AHF showed an RR (95% CI) of 1.143 (0.299–4.367) with p=0.845, showing that a history of T2DM did not have a significant effect on AHF, which was estimated to be due to mild T2DM or controlled T2DM, causing the ability of the incretin hormone in producing GLP-1 to still be intact, having a cardioprotective effect in preventing AHF. A decrease in the incretin hormone causing the decrease of GLP-1 secretion only happens in uncontrolled T2DM with insulin resistance or in dysfunction of the B cells of the pancreas.[22]

Statistical analysis between GLP-1 plasma concentrations towards AHF had a RR (95% CI) of 2.881 (0.729–11.381) with p – 0.127. The comparison of GLP-1 below COV (<20.135 pg/mL) that had AHF and didn't acquire AHF were 11 patients (64.7) and 6 patients (35.3%), even though there was a tendency for AHF patients to have lower GLP-1 plasma concentrations, they were not statistically significant, this might be due to another factor effecting the decrease if GLP-1 concentrations such as obesity, use of hypoglycemic causing drugs (Metformin), extensive myocardial infarct, etc.; on the contrary, the cause of high GLP-1 plasma levels are due to oral consumption of certain food, therapy (insulin GLP-1 agonist, DPP-4 and DPP-4 inhibitor and after the Roux-en-Y Gastric Bypass (RYGB) or Duodenal-Jejunal Bypass (DJB).[9]

This study has several limitations, the first one being the studies design that does an analysis in one sampling. This may cause a bias due to the variables not reaching the peak, due to a delay or wrong procedure during sampling. The minimal sample size in this study cannot be generalized to the public population. Many variables are involved in the pathogenesis of AHF, the possibility of interaction between variables as a risk factor of cardiac disease, and the interaction between at least two risk factors to obtain HF that affects the statistical significance. The fluctuation of GLP-1 levels in the acute phase of AMI is still unknown, causing difficulties in determining the onset of AHF. Echocardiography is also done on the second day, causing limitations to the implementation of this study's results in clinical practice. These limitations can be a consideration if further studies with similar topics will be conducted.

CONCLUSIONS AND SUGGESTIONS

The decrease of plasma GLP-1 under the cut-off value does not have a predictive value towards AHF in patients with AMI. This confirms that currently plasma GLP-1 cannot be used to predict the AHF complication following AMI. Further study with larger sample size and serial examination of various blood parameters and GLP-1 is needed.

REFERENCES

1. Cahill TJ, Kharbanda RK. Heart failure after myocardial infarction in the era of primary percutaneous coronary intervention: Mechanism incidence and identification of patients out risk. World J Cardiol, 2017; 9(5): 407-15.
2. Taguchi E, Konami Y, Inoue M, Suzuyama H, Kodema K, *et al*. Impact of KILLIP classification on acute myocardial infarction: Data from the SAIKUMA registry. Heart and Vessels, 2017; 32(1): 1439-47.
3. Bahit MC, Kocher MD, Granger CB. Post-myocardial infarction heart failure. Clin Sci, 2018; 6(3): 179-86.
4. Coats AJS. Common co-morbidities in heart failure-diabetes, functional mitral regurgitation and sleep apnoe. Int J Heart Failur, 2019; 1(1): 25-41.
5. Garcia MI, Torres JFM. GLP-1 receptor agonists and cardiovascular disease in patients with type 2 diabetes. J Diabetes Res, 2018; 1(2): 1-12.
6. Andrikou E, Tsioufis C, Andrikou I, Leontsinis I, Tousoulis D, Papanas N. GLP-1 receptor agonists and cardiovascular outcome trials: An update. Hellenic J Cardiol, 2019; 60(1): 347-51.
7. Gilbert MP, Pratley RE. GLP-1 analogs and DPP-4 inhibitors in type 2 diabetes therapy review of head to head clinical trials. Front Endocrinol, 2020; 11(178): 1-13.
8. Scheen AJ. GLP-1 receptor agonists and heart failure in diabetes. Diabetes Metab, 2017; 43(12): 14-19.
9. Zykov VA, Tuchina TP, Lebedev DA, Krylova IB, Babenko AY, *et al*. Effect of glucagon-like peptide 1 analogs in combination with insulin on myocardial infarct size in rats with type 2 diabetes mellitus. World J Diabetes, 2018; 9(9): 149-56.
10. Gerber Y, Weston SA, Sarano ME, Berardi C, Chamberlain AM, *et al*. Mortality associated with heart failure after myocardial infarction. Circ Heart Fail, 2016; 9(1): 1-9.

11. Rahayu MS. Hubungan indeks massa tubuh dengan penyakit jantung koroner di Rumah Sakit Umum Cut Meutia Kabupaten Aceh Utara. MJMA, 2015; 6(1): 9-16.
12. Simonenko M. Obesity paradox in heart failure: A matter of debate. Eur J Prev Cardiol, 2019; 1(1): 1-3.
13. Iskandar, Hadi A, Alfridsyah. Faktor risiko terjadinya penyakit jantung koroner pada pasien Rumah Sakit Umum Meuraxa Banda Aceh. AcTion Journal, 2017; 2(1): 32-42.
14. Hedayatnia M, Asadi Z, Feyzabadi RZ, Kharasani MY, Ghazizade H, et al. Dyslipidemia and cardiovascular disease risk among the MASHAD study population. Lipids Health Dis, 2020; 19(42): 1-11.
15. Ahmed AA, Patel K, Nyaku MA, Kheirbek RE, Bittner V, *et al*. Risk of heart failure and death after prolonged smoking cessation role of amount and duration of prior smoking. Circ Heart Fail, 2015; 8(1): 694-701.
16. Yudanardi MRR, Setiawan AA, Sofia SN. Hubungan tingkat adiksi merokok dengan derajat keparahan aterosklerosis pada pasien penyakit jantung koroner. J Kedokt Diponegoro, 2016; 5(4): 1207-13.
17. Perry HM, Deshmukh H, Levin D, Zuydam NV, Elder DHJ, *et al*. Both high and low HbA1c predict incident heart failure in type 2 diabetes mellitus. Circ Heart Fail, 2015; 8(1): 236-42.
18. Alhabib KF, Gamra H, Almahmeed W, Hammoudeh A, Benkheddah S, Al Jarallah M, Al-Motarreb A, Alquraishi M, Sobhy M, Yousif MG, Alkindi F. Acute myocardial infarction and acute heart failure in the Middle East and North Africa: Study design and pilot phase study results from the PEACE MENA registry. PLos One, 2020; 15(7): e0236292.
19. Wellings J, Kostis JB, Sargsyan D, Kostis WJ, Cabrera J. Risk factors and trends in incidence of heart failure following acute myocardial infarction. Am J Cardiol, 2018; 1(2): 1-15.
20. Blecker S, Park H, Katz SD. Association of HbA1c with hospitalization and mortality among patients with heart failure and diabetes. BMC Cardiovasc Disord, 2016; 16(99): 1-8.
21. Villanueva P, Alfonso F. Heart failure in the eldery. J Geriatr Cardiol, 2016; 13(1): 115-17
22. Lee YS, Riopel M, Cabrales P, Bandyopadhyay GK. Hepatocyte-specific HIF-1α ablation improves obesity-induced glucose intolerance by reducing first-pass GLP-1 degradation. Science Advances, 2019; 5(7): eaaw4176.