Growth Differentiation Factor-15 (GDF-15) as a Predictor of Major Adverse Cardiac Event in Acute Myocardial Infarction Patients

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ABSTRACT

***Background*:** *Growth Differentiation Factor-15 (GDF-15) has emerged as a biomarker that capable to predicting cardiovascular events. Recent studies suggest that GDF-15 is elevated in patients with acute myocardial infarction (AMI), but the prognostic remains incompletely defined. This study aimed to investigate the role of GDF-15 levels with major cardiac adverse events (MACE) on three months follow up in patients with AMI.* ***Methods*:** *This cohort study was conducted from November 2020 until May 2021 at Dr. Moewardi Hospital. GDF-15 was measured at admission, clinical data was collected and 3 months follow up events was registered. Prognostic value of GDF-15 and hazard ratio between high and low GDF-15 level were analyzed.* ***Results*:** *A total of 64 AMI patients were included in this study. MACE at three months follow-up occurred in 26.5% of patients. In multivariate analysis, GDF-15 was independently associated with risk of MACE at 3 months follow up (OR 1.501; p = 0.003). The cut-off point value of GDF-15 was analyzed with the ROC curve, obtained 2256 pg/mL which has a sensitivity of 94.1% and a specificity of 73.8% (area under the curve (AUC) 86.2%; 95% CI 0.768-0.956). Risk model with Kapplan Meier showed significant association between high GDF-15 levels (≥ 2256 pg/mL) and the incidence of MACE at 3 months follow up (HR 12.029; 95% CI 3.429- 42.197; p <0.001)* ***Conclusion*:** *In patients with AMI, high level of GDF-15 was significantly associated with the risk of MACE at 3 months of observation.*

***Keywords*:** *acute myocardial infarction, growth differentiation factor-15, major adverse cardiac event.*

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of mortality worldwide, have brought heavy burden to social healthcare and individuals. Seven million people die every year, accounting for 12.8% of all deaths. Data from the World Health Organization (WHO) in 2012 showed that 17.5 million people died from cardiovascular disease, or 31% of the 56.5 million deaths worldwide. This number was estimated to continue to increase to 23.6 million deaths in 2030.[1] In this case, data from Dr. Moewardi General Hospital, Surakarta, Indonesia, revealed that the death rate from acute coronary syndrome (ACS) from 2014-2018 reached 15.9%.[2]

More specifically, concerning myocardial infarction, tissue necrosis following myocardial infarction is often followed by a later incidence of

heart failure, myocardial rupture, or arrhythmias. In this regard, early management of ischemia to prevent myocardial necrosis with medications, such as fibrinolytic, percutaneous coronary intervention, and coronary artery bypass surgery, has improved the clinical outcome of patients with ACS. Biomarkers have an essential role in establishing the diagnosis and prognostication to predicting future cardiovascular risk. Various emerging biomarkers have been known to have a vital role in the pathophysiology of ACS.[3]

Growth Differentiation Factor-15 (GDF-15) has emerged as a promising biomarker for predicting cardiovascular events in later life. GDF-15 is a superfamily of transforming growth factors (TGF-β). It is synthesized as a 40 kDa propeptide with an N-terminal propeptide and a mature C-terminal domain of GDF-15.[4] Under physiological conditions, GDF-15 is slightly expressed by endothelial cells and macrophages. GDF-15 increases during the inflammatory process and is associated with cardiometabolic risk.[5] In previous studies, GDF-15 levels link to the adverse cardiovascular events across a spectrum of CVD conditions including heart failure (HF), chest pain, acute coronary syndromes (ACS), stable ischemic heart disease, stroke and atrial fibrilation.[6,7] The potential role of GDF-15 may attribute to the earlier diagnosis, risk stratification and prognosis assessment. However, limited research have analyzed the association between GDF-15 levels and all-cause mortality or heart failure on the long-term follow-up. Hence, this study aimed to analyzed relationship between GDF-15 levels with survival and major cardiovascular events (MACE) in patients with post acute myocardial infarction (AMI).

METHODS

Research Subjects

The research subjects were AMI patients who underwent treatment at the Intensive Cardiovascular Care Unit (ICVCU) Dr. Moewardi General Hospital, Surakarta, Central Java from November 2020 to April 2021. The researchers excluded patients with severe comorbidities, such as malignancy, chronic renal failure, stroke, and severe sepsis.

Research Design

This cohort analytic study applied a prospective design. Data were acquired from the intensive cardiovascular care unit (ICVCU) and cardiology ward at RSUD Dr. Moewardi, Surakarta, Central Java. The Ethics Committee of Dr. Moewardi General Hospital approved this study's protocol with ethical approval No. 1.287/XII/HREC/2020 issued on 17th November 2020.

Acute myocardial infarction (AMI) is defined as presence of acute myocardial injury detected by abnormal cardiac biomarkers in the setting of evidence of acute myocardial ischemia of at least one value above the 99th percentile of the upper reference limit, accompanied by at least one of the following: 1) Presence of a complaint of acute myocardial ischemia; 2) ECG changes as evidence of new ischemia; 3) Pathological Q wave formation; 4) Imaging evidence of loss of myocardial viability or the presence of new regional myocardial wall motion abnormalities consistent with the etiology of ischemia.[8] Meanwhile, major adverse cardiac event/MACE is defined as the presence of death, reinfarction, and nonfatal heart failure events requiring rehospitalization.[9,10]

In this study, GDF-15 was obtained from venous blood samples of patients with AMI at the time of admission and measured using the enzyme-linked immunosorbent assay (ELISA) with pg/mL units. Cut-off points for GDF-15 were determined utilizing receiver operating characteristic (ROC) analysis. MACE was followed up to 90 days after admission by reviewing medical records and communicating directly with patients.

Statistical Analysis

Statistical analysis was performed utilizing the Statistical Package for the Social Sciences (SPSS) 22 (IBM, Chicago, USA). A Chi-square test was used to compare two categorical variables, while an independent t-test or Mann-Whitney test was employed to compare data with categorical and numerical variables. Significant variables were included in multivariate logistic regression analysis. The cut-point value of the optimal GDF-15 level to predict MACE occurrence was analyzed by the receiver operating characteristic (ROC) curve. Survival

analysis was carried out using the log-rank test on the Kaplan-Meier curve. The p-value <0.05 were considered to be statistically significant.

RESULTS

In total there were 70 patients with acute myocardial infarction who were the subjects of the study obtained by consecutive sampling that met the inclusion criteria. There were 3 patients with chronic renal failure, 2 patients with severe sepsis, and 1 patient with stroke who were excluded in this study. Demographically, the patient's age who were the subjects of this study ranged from 38 years to 86 years, with a mean value of 58.5 SD 9.5 years. A total of 48 people were male, or 66.66%, while the remaining 16 people, or 33.33%, were female. The majority of subjects had a body mass index (BMI) of *normoweight* or normal (16.35-33.20).

Hypertension was the most dominant risk factor in this study population. A total of 41 (64%) people were stated to have a history of hypertension. In the subjects of this study, 48 patients (75%) were diagnosed with STEMI, and 16 patients (25%) were diagnosed with NSTEMI.

MACE on Research Subjects

MACE was followed up to 90 days after hospital admission and was recorded in 17 subjects (26.5%), with the proportions of death, the incidence of acute heart failure leading to rehospitalization, and reinfarction of 14.1%, 9.3%, and 3.1%, respectively (**Figure 1**). Characteristics of research subjects based on the occurrence of MACE during hospitalization and MACE in 3-month observation are presented in **Table 1**.

Patients with MACE at 3-months follow up had a higher mean GDF-15 level than patients without MACE (3736 SD 1857 vs. 2348 SD 1500). When the bivariate analysis was performed, the parameters that were significant for the incidence of MACE were GRACE score (p=0.033), estimated glomerular filtration rate (eGFR) (p=0.037), urea (p=0.037), GDF-15 (p<0.001), percutaneous coronary intervention (PCI) (p=0.041), and the medication of ß-Blockers (p=0.039) **(Table 2).**

Table 1. Subject's Characteristic Based on MACE.

Variables	MACE in 3 months follow up	
	MACE (+) (n=17)	MACE (-) (n=47)
Male	10 (58.8%)	38 (80.9%)
Age (years)	61.41 SD 15.28	59.68 SD 11.28
Onset (hours)	15 (1-124)	24 (1.5-168)
BMI (kg/m^2)	24.27 SD 3.62	23.44 SD 2.97
SBP (mmHg)	128 (78-179)	126 (90-215)
DBP (mmHg)	80 (42-124)	79 (50-130)
Heart Rate (x/m)	68 (40-124)	77 (52-130)
Resppiratory rate (x/m)	20 (16-32)	20 (0-30)
TIMI score	5 (2-9)	3 (1-10)
GRACE score	128.7 SD 36.79	105.66 SD 37.62
Kilip > I	8 (47.1%)	18 (38.3%)
Previous medical history		
Hypertension	10 (58.8%)	31 (66.0%)
DM	3 (17.6%)	15 (31.9%)
Stroke	0 (0.0%)	2 (4.3%)
Smoking	7 (41.2%)	23 (48.9%)
Dyslipidemia	1 (5.9%)	2 (4.3%)
Previous CAD	6 (35.3%)	8 (17.0%)
Hb (g/dL)	13.20 (8.5-15.6)	13.8 (9.8 -17.2)
Leucocyte (1000/uL)	14.5 (6.59-41)	11.6 (4.8-19.5)
Thrombocyte (1000/uL)	200 (41.5-346)	239 (2.5-427)
Glucose (mg/dL)	122 (86-388)	116 (69-388)
Urea (mg/dL)	53 (10-85)	32 (1.1 -162)
Creatinine (mg/dL)	1.2 (0.6-10)	1 (0.3-18)
eGFF (ml/min/1.73 m^2)	13.19 SD 2.45	43.56 SD 2.74
Na (mmol/L)	133.94 SD 4.84	134.36 SD 4.19
K (mmol/L)	3.6 (3-5.1)	3.8 (2.9-6.3)
hs-Trop I (ng/L)	15464 (25-40000)	18803 (7-40000)
Total Cholesterol	152 (75-188)	160 (89-307)
LDL (mg/dL)	100 (40-180)	126 (59-327)
HDL (mg/dL)	35.19 SD 16.19	35.72 SD 12.20
GDF-15 (pg/nL)	6000 (1738-6000)	2256 (720-6000)
LVEF (%)	38.71 SD 10.73	43.60 SD 9.26
Treatment		
PCI	5 (29.4%)	37 (78.7%)
Fibrinolitic	3 (17.6%)	12 (25.5%)
Anticoagulant	17 (100.0%)	47 (100.0%)
DAPT	17 (100.0%)	47 (100.0%)
Statin	17 (100.0%)	47 (100.0%)
ß-Blocker	10 (58.8%)	40 (85.1%)
ACE inhibitor	14 (82.4%)	40 (85.1%)

Table 2. Bivariate Analysis of MACE at 3-months Follow Up.

Variables	MACE in 3 months follow up		*p*
	MACE (+) (n=17)	MACE (-) (n=47)	
Male	10 (58.8%)	38 (80.9%)	0.103
Age (years)	61.41 SD 15.28	59.68 SD 11.28	0.625
Onset (hours)	15 (1-124)	24 (1.5-168)	0.144
BMI (kg/m2)	24.27 SD 3.62	23.44 SD 2.97	0.358
SBP (mmHg)	128 (78-179)	126 (90-215)	0.681
DBP (mmHg)	80 (42-124)	79 (50-130)	0.951
Heart Rate (x/m)	68 (40-124)	77 (52-130)	0.245
Resppiratory rate (x/m)	20 (16-32)	20 (0-30)	0.418
TIMI score	5 (2-9)	3 (1-10)	0.063
GRACE score	128.7 SD 36.79	105.66 SD 37.62	0.033*
Kilip > I	8 (47.1%)	18 (38.3%)	0.529
Previous medical history			
Hypertension	10 (58.8%)	31 (66.0%)	0.599
DM	3 (17.6%)	15 (31.9%)	0.353
Stroke	0 (0.0%)	2 (4.3%)	1.000
Smoking	7 (41.2%)	23 (48.9%)	0.583
Dyslipidemia	1 (5.9%)	2 (4.3%)	1.000
Previous CAD	6 (35.3%)	8 (17.0%)	0.170
Hb (g/dL)	13.20 (8.5-15.6)	13.8 (9.8 -17.2)	0.178
Leucocyte (1000/uL)	14.5 (6.59-41)	11.6 (4.8-19.5)	0.215
Thrombocyte (1000/uL)	200 (41.5-346)	239 (2.5-427)	0.082
Glucose (mg/dL)	122 (86-388)	116 (69-388)	0.390
Urea (mg/dL)	53 (10-85)	32 (1.1 -162)	0.037*
Creatinine (mg/dL)	1.2 (0.6-10)	1 (0.3-18)	0.072
eGFF (ml/min/1.73 m^2)	13.19 SD 2.45	43.56 SD 2.74	0.026*
Na (mmol/L)	133.94 SD 4.84	134.36 SD 4.19	0.735
K (mmol/L)	3.6 (3-5.1)	3.8 (2.9-6.3)	0.988
hs-Trop I (ng/L)	15464 (25-40000)	18803 (7-40000)	0.888
Total Cholesterol	152 (75-188)	160 (89-307)	0.085
LDL (mg/dL)	100 (40-180)	126 (59-327)	0.065
HDL (mg/dL)	35.19 SD 16.19	35.72 SD 12.20	0.888
GDF-15 (pg/nL)	6000 (1738-6000)	2256 (720-6000)	<0.001*
LVEF (%)	38.71 SD 10.73	43.60 SD 9.26	0.079
Treatment			
PCI	5 (29.4%)	37 (78.7%)	0.041*
Fibrinolitic	3 (17.6%)	12 (25.5%)	0.740
Anticoagulant	17 (100.0%)	47 (100.0%)	-
DAPT	17 (100.0%)	47 (100.0%)	-
Statin	17 (100.0%)	47 (100.0%)	-
ß-Blocker	10 (58.8%)	40 (85.1%)	0.039*
ACE inhibitor	14 (82.4%)	40 (85.1%)	1.000

Multivariate analysis was performed by logistic regression, showed only eGFR (OR 1.011; p=0.049; 95% CI 1.000-1.022) and GDF-15 (OR 1.501; p=0.001; 95% CI 1.000-1.602) were independent predictors of the occurrence of MACE within the 3-months follow-up in AMI patients (**Table 3**).

Table 3. Multivariate Analysis of MACE Predictors in 3-month Observation.

Variables	OR	95%CI	p-value
GRACE score	0.999	0.978-1.021	0.956
GFR	1.011	1.000-1.022	0.049*
Urea	0.983	0.954-1.013	0.263
GDF-15	1.501	1.000-1.602	0.003*
PCI	0.102	0.016 -1.032	0.054
ß-Blocker	0.621	0.083 -4.644	0.642

Note: *p<0.005

On the ROC curve, GDF-15 levels had an AUC of 0.862 (p<0.001; 95% CI 0.768-0.956) in predicting MACE at 3-months follow-up (**Figure 1**). From this ROC curve, it was found that the cut-off point for GDF-15 was 2655 at a sensitivity of 91.7% and a specificity of 73.8%. This cut-off value had a positive predictive value (NDP) of 59.3% and a negative predictive value (NDN) of 93.7%.

Furthermore, patients were divided into two groups based on GDF-15 levels. GDF-15 levels were categorized as high if more than 2655 pg/mL, and GDF-15 levels were categorized as low if <2655 pg/mL. In all study subjects, there were 32 patients with high GDF-15 levels and 32 patients with low GDF-15 levels.

The analysis to determine the difference in MACE in the group with high and low GDF-15 levels is described in **Table 4**. In this table, it appears that there was a significant difference in MACE in the three months follow-up between groups of patients with high and low GDF-15 levels (48.3% vs 7.5%, p< 0.001) (**Table 4**).

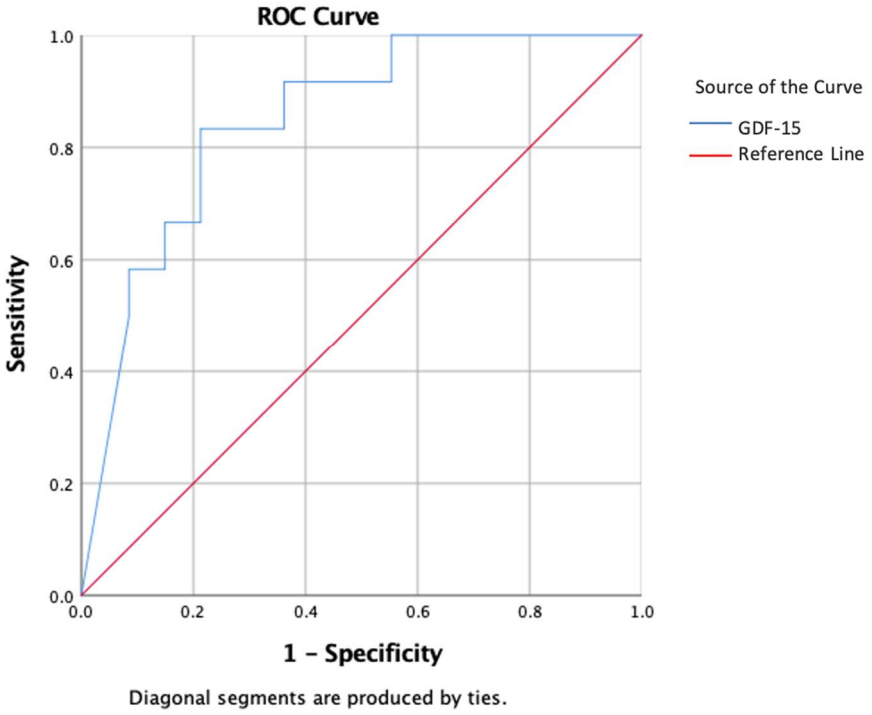

Figure 1. ROC Curve of GDF-15 to MACE at 3 Months Follow-up.

Table 4. Association Between MACE with High and Low Levels of GDF-15.

Variables	GDF-15 High ≥2655 (n=32)	GDF-15 Low <2655 (n=32)	p-value
MACE in three months	19 (58.3%)	2 (7.5%)	<0.001*
All Cause mortality	12 (37.5%)	0 (0.0%)	<0.001*
Acute heart failure	5 (16.7%)	2 (5.0%)	0.121
Reinfarction	2 (8.3%)	0 (0.0%)	0.064

Note: *p<0.005

Kaplan-Meier curve analysis was performed, to determine the difference in survival between patients with high (≥2655 pg/mL) and low (<2655 pg/mL) GDF-15 levels. At three months follow-up, more frequent MACE events were found in the group with high levels of GDF-15 with a hazard ratio (HR) of 12,029 (95% CI 3,429-42.197; p<0.001). It means that high levels of GDF-15 had a 12-fold risk of causing MACE within three months post-AMI (**Figure 2**).

DISCUSSION

In this study, the researchers analyzed the role of GDF-15 as a predictor of MACE occurrence in patients with acute myocardial infarction at 3-months follow-up. The researchers reported three main findings. First, this study's data indicated a difference between high and low levels of GDF-15 in MACE occurrence. A higher GDF-15 value was associated with an increased risk of developing MACE after a 3-month observation. In line with research studies Eitel et al, Bonaca et al, and Hagstrom et al.[11-13] GDF-15 has been associated with an increased risk of all-cause mortality, reinfarction, heart failure, and major hemorrhage in post-AMI.[9]

Second, this study revealed that GDF-15 was a strong predictor of MACE occurrence in AMI patients on 3-month follow-up, along with other clinical factors, namely GFR. Furthermore, Peiro and colleges has found that the addition of the variable GDF-15 level to the clinical variables, such as age, GRACE score, and LVEF <40%, had additional prognostic value with a corresponding and significant increase in the ROC curve. Furthermore, GDF-15 provides better prognostic information than peak cardiac troponin I (cTnI).[9]

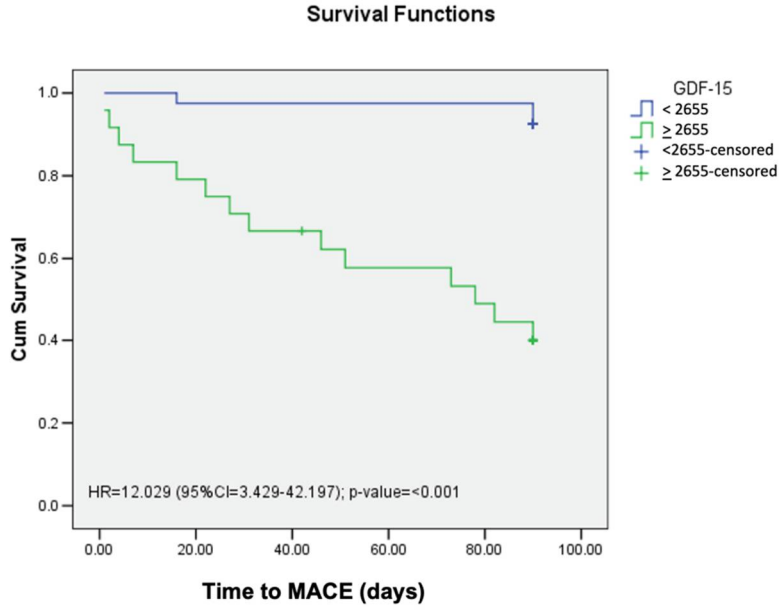

Figure 2. Kapplan-Meier curve showing the survival between patients with high and low levels of GDF-15 to MACE at 3 months follow-up

The researchers also found that the GDF-15 cut-off value for MACE risk was 2655 pg/mL with the ROC curve. This figure is quite different from previously reported, where, in previous studies, the majority used a cut-off point of 1800 pg/mL.[7,10,14] Study by Walter and collegues tried to find the cut-off point with the ROC curve, obtained a value of 1560 ng/L.[15] It might be because, in this study, the population included in the study was patients with the suspected acute coronary syndrome, with or without acute myocardial infarction. Meanwhile, in the current study, only patients with acute myocardial infarction were included. Besides, it might also be due to racial and ethnic differences. With this research, it is hoped that it will find the appropriate cut-off point for the Indonesian population.

The cut-off value of 2655 in current study had a sensitivity of 94.1% and a specificity of 73.8%. Slightly different from the study by Peiro and collegues, the cut-off value in patients with AMI was 1759 ng/L with 100% sensitivity for predicting death within 6.5 years. This study also explained that the advantage of GDF-15 in predicting mortality compared to hs-Trop I was statistically significant.[9]

Third, the researchers reported that GDF-15 was one factor in assessing the survival of patients with AMI. In the current analysis, high levels of GDF-15 (≥2655 pg/mL) tended to develop MACE at 3-month follow-up with a hazard ratio (HR) of 12,029 (95% CI 3,429-42.197; p<0.001). These results align with previous studies, which revealed that high levels of GDF-15 (>1800 ng/L) had a tenfold risk of death and a fourfold MACE at 6.5 years post-AMI.[9] The same results were obtained in a previous study by Khan and collegues, that GDF-15 was an independent predictor of MACE occurrence within one year in patients with AMI.[10]

Several factors explain the increase of GDF-15 concentration in post-AMI patients. The first is the tissue response to inflammation, which appears to be responsible for most of the discharge observed in the acute phase and will include local reactions to myocardial ischemia, volume and pressure overload, and systemic responses to myocardial injury and other organ disturbances (**Figure 3**).[4]

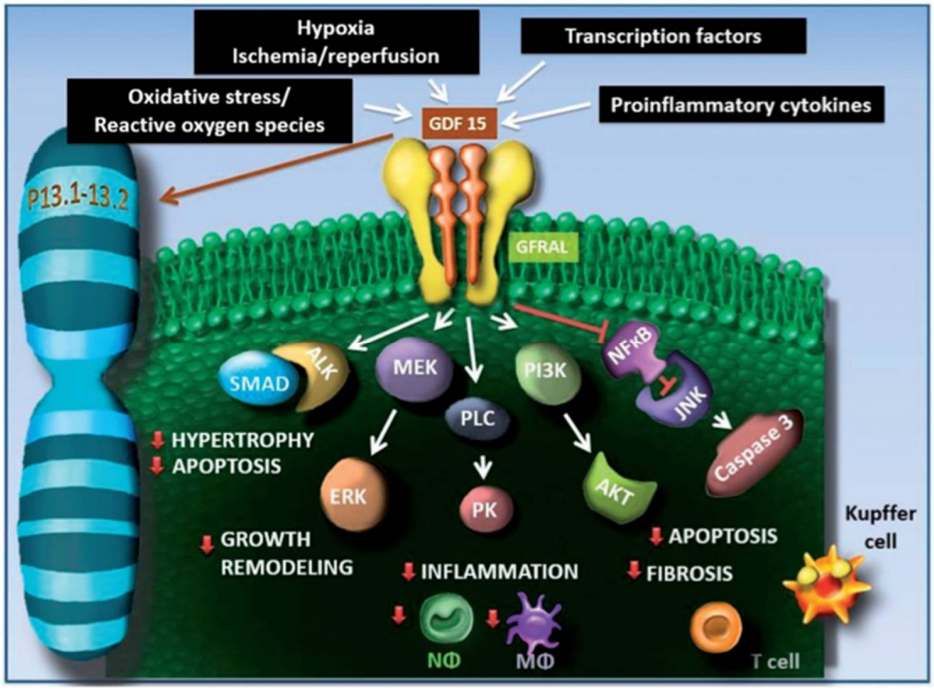

Figure 3. GDF-15 expression is increased in several responses to signals as diverse as oxygen deprivation (eg oxidative stress, hypoxia, and anoxia); inflammation and acute tissue injury [proinflammatory cytokines such as TNF-, IL-1β, IL-6, macrophage colony stimulating factor (M-CSF), and NF-κB]. Although its exact mechanism of action has not been clarified, GDF-15 can function as an autocrine, anti-inflammatory, and cell repair factor that is secreted in proportionate amounts in acute and chronic tissue injury. [4]

These factors explain the strength of GDF-15 as a short-term predictor of MACE. On the other hand, a lower but persistent increase in circulating GDF-15 may appear to reflect the chronic inflammatory background. In a cohort study of community-dwelling individuals, in patients with stable coronary heart disease[12] and heart failure patients[17], an increase in GDF-15 concentrations was a predictor of long-term cardiovascular events and all-cause mortality.

GDF-15 under physiological conditions is only expressed in small amounts, which is increased in the presence of ischemia or reperfusion as endogenous protection against ischemia and reperfusion with a cardiomyopathic apoptotic effect. Thus, GDF-15 can also be conceptualized as a marker of biological age and chronic heart disease burden[18], which may be a key determinant for long-term outcome. In this regard, according to some clinicians, GDF-15 could identify ACS patients who would benefit most from invasive strategies[18], more intense P2Y12 inhibitors[19], or high-dose statin therapy.[20] In addition, reflecting the connection between ischemic risk and bleeding, GDF-15 levels at admission have been identified as an equally strong and independent predictor of major bleeding and ischemic complications during the 12-month observation in ACS patients from the PLATO study.[13]

CONCLUSION

In this study, we found differences in major cardiovascular events (MACE) between patients with high GDF-15 levels and low GDF-15 levels at the 3-month follow-up in acute myocardial infarction patients. Thus, high levels of GDF-15 could be a predictor of the occurrence MACE at 3-month follow-up in acute myocardial infarction patients.

Further studies with bigger sample, multicenter, serial measurements, and longer observation times are needed to add strength to the study and establish the role of GDF-15 as a predictor of MACE in patients with myocardial infarction.

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