Relationship between Plasma neuregulin-1

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Relationship between Plasma Neuregulin-1 and MDA Levels with Severity of CAD

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Abstract

BACKGROUND: Neuregulins (NRGs) are one of the epidermal growth factors (EGF) superfamily, which released in cellular injuries, such as neurons and myocardial cells. Neuregulin-1β (NRG-1β) could be activated when stress happens to myocardial cells, acting as a survival factor to repair the injury. Malondialdehyde (MDA) is also produced during oxidative stress in cardiac injury. In vivo study of myocardial cells in rats and dogs that got ischemic, dilated, and viral cardiomyopathy showed that NRG-1 could improve the injured cardiac performance, attenuated pathological changes, and prolonged survival of the cells.

AIM: We aimed to observe NRG-1 levels in CAD patients in Indonesia, mainly focused in Minang ethnicity. This study also analyzes the relationship between NRG-1 and MDA with CAD's severity.

METHODS: We measured plasma NRG-1 in 61 nondiabetic patients within 38–82 years old range with STEMI, NSTEMI, and UAP.

RESULTS: We found their plasma NRG1, respectively, was 10.3 (1.9–38.2) ng/ml, 14.3 ± 7.2 ng/ml, and 7.05 (4.5–0.4) ng/mL. Plasma NRG 1 increased in AMI patients.

CONCLUSION: This study concludes that NRG1's activated during cardiac cells injury, in any AMI.

Introduction

About one-third of the world population died because of coronary artery disease (CAD), joined with cerebrovascular diseases [1]. The level of CAD's severity related to some biologic factors, such as inflammatory cytokines and lipoproteins, that influence atherosclerosis and angiogenesis processes. The relationship between vascular growth factor and CAD's severity has not been clearly identified yet. Validated biomarkers are important screening methods to help patients with heart risks and heart diseases related symptoms. These biomarkers reflect the CAD's severity and ischemic heart incident [2].

Neuregulin-1 (NRG-1) is an angiogenic and growth factor activated by stress, including oxidative stress. NRG-1 is activated by ischemia and physical activity in animals. NRG-1 works through the ErbB receptor in controlling the cell's survival, growth, metabolism, and angiogenesis. Oxidative stress and inflammation play a significant role in the atherosclerosis process of CAD. A previous study has shown that neuregulin-1 is a prominent angiogenic factor in diabetic cardiomyopathy, whereas the relationship between neuregulin-1 and MDA plasma level has not been investigated [3]. The malondialdehyde (MDA) was produced during oxidative stress on lipid peroxidation [2]. MDA levels and H-CRP are significantly increasing in CAD patients [4]. Previous studies show that plasma NRG-1 levels were higher in patients with stress-induced ischemia [2]. However, the underlying physiologic and pathologic factors influencing the development of NRG-1 could improve the injured cardiac performance unclear. High levels of NRG-1 relate to worsen symptoms of heart failure, and bad prognosis, especially in ischemic heart diseases [5]. NRG-1 protects cells from oxidative stress exposure, such as hydrogen peroxide and also hydrogen peroxide induced-apoptosis. Further research is needed to understand the correlation between NRG-1 and ischemic [6].

There is still a few data in NRG-1 and MDA relationship with CAD's severity. NRG-1 has been shown to have potential in treating patients with heart cell death. There is not any data about NRG-1 levels in CAD patients in Indonesia. This research is a preface

study to observe NRG-1 levels in CAD patients in Indonesia, mainly focused in Minang ethnicity. This study also analyzes the relationship between NRG-1 and MDA with CAD's severity.

Materials and Methods

The study population consisted of a retrospective of 61 nondiabetic patients who underwent coronary angiography due to either STEMI, NSTEMI, or UAP from July to November 2017 from an academic referral center. The samples were taken in 24 h after primary catheterization and without regard to the onset of a heart attack. The CAD severity was further characterized in these subgroups using the SYNTAX score, which accounts for lesion location, degree of stenosis, and the number of vessels involved [7]. The study was performed by the Committee of the Research ethics of the Faculty of Medicine, Universitas Andalas, with number 329/KEP/FK/2017. All patients were informed, and consent was obtained.

Plasma NRG-1 measurement

Human NRG-1(Neuregulin 1) ELISA Kit from Elabscience® was used to assay plasma NRG-1 levels according to the manufacturer's instructions. The measurement was held in the Biomedicine Laboratory of Faculty of Medicine, Universitas Andalas.

Plasma MDA measurement

Plasma MDA levels were measured using spectrophotometry in the Biochemistry Laboratory of Faculty of Medicine, Universitas Andalas.

CAD severity

CAD severity was measured by the SYNTAX score (SYNergy between PCI with TAXUS™ and Cardiac Surgery). SYNTAX score is an available measurement tool to make the medical decision in managing CAD's patients mainly focused in choosing actions based on coronary anatomy. Moderate-high severity of CAD is defined if SYNTAX score >22 and low severity is defined if SYNTAX score ≤ 22 [7].

Analysis

Categorical variables were compared by the Chi-square test, while t-test and Mann–Whitney used for the numerical variable. Statistical analysis was performed with SPSS 20.0. Data are statistically significant results with $p < 0.05$.

Results

There were 70 patients with CAD who were included in this study, 9 of them were excluded since they were diagnosed by diabetes mellitus. A total of 61 patients were measured for NRG-1 plasma and MDA. In this study, most patients were male of 40–64 years old. Table 1 shows 39 patients with high severity of CAD based on the SYNTAX score had a higher lipid profile level, and there were no significant differences to 22 patients with low severity of CAD (SYNTAX≤22). Hypertension, dyslipidemia, and smoking are the most risk factor for CAD in these patients. STEMI was the most diagnosed of all (67.2%). There were no significant differences in gender, age, diagnosis, risk factor, blood glucose, and BMI. Lipid profiles, including TC, TG, LDL-C, and HDL-C, were not significantly different between the two groups. Plasma NRG-1 levels showed a higher value in moderate to severe CAD patients (median 13.59) than mild CAD patients (median 10.97). There were no significant differences between plasma NRG-1 levels in mild and moderate to severe CAD. Higher levels of plasma NRG-1 were shown in STEMI (Table 2). Levels of MDA plasma were higher in the group with SYNTAX >22 (2.61 ± 0.62) than in the group with SYNTAX ≤22 (2.61 ± 0.62). The higher levels of plasma MDA were shown in UAP and NSTEMI (Table 3). In this study, shown in Figure 1, we found that mean MDA levels in high severity patients are higher than mild to moderate severity patients, but not statistically significant (3.02 ± 0.69 vs. 2.61 ± 0.62, $p = 0.074$).

Table 1: Patient characteristics

Characteristics	All patients (n,%)	SYNTAX		p value
		<22 (n = 22)	>22(n = 39)	
Gender				
Male	54 (88.5%)			
Female	7 (11.5%)			
Age	56.4 ± 8.7	56.4 ± 6.3	56.6 ± 10.1	0.924
< 40 years old	1 (1.6%)			
40–64 years old	50 (81.9%)			
> 65 years old	10 (16.5%)			
Diagnosis				
UAP	6 (9.8%)	0	6	
NSTEMI	14 (23%)	7	7	
STEMI	41 (67.2%)	15	26	
Risk factors				
Hypertension	34 (55.7%)	12	22	0.888
Family history	8 (13.1%)	3	5	0.928
Dyslipidemia	33 (54.1%)	13	20	0.559
Menopause (n=7)	1/7 (14.3%)	0	1	1.000
Smoking	42 (68.9%)	14	28	0.509
Lipid profiles				
Total cholesterol		176.3 ± 41.4	206.8 ± 69.2	0.363
HDL		31.5 (14-43)	40.4 (22-87)	0.335
LDL		123.4 ± 38.6	134.9 ± 59.6	0.499
Triglycerides		121.4 ± 38.3	140.8 ± 50.2	0.210
Blood glucose		132.8 ± 33.2	121.1 ± 22.6	0.268
HbA1c		5.4 (5-5.6)	5.7 (5-6.3)	0.000
BMI		23.7 ± 2.5	24 ± 2.5	0.395

Table 2: Plasma NRG-1 levels in ACS patients

NRG-1 levels	Median (min-max)	p value
Syntax		
≤ 22	10.97 (1.15–32.25)	0.775
> 22	13.59 (1.91–38.2)	
Diagnosis		
UAP and NSTEMI	13.86 (1.15–29.53)	0.634
STEMI	10.31 (1.91–38.2)	

Table 3: Plasma MDA Levels in ACS patients

Malondialdehyde level	Mean ± SD	p value
Syntax		
≤ 22	2.61 ± 0.62	0.074
> 22	3.02 ± 0.69	
Diagnosis		
UAP and NSTEMI	2.95 ± 0.82	0.593
STEMI	2.82 ± 0.64	

Discussion

The main finding of this study was that patients with CAD plasma NRG-1 did not significantly associate with CAD severity (SYNTAX score). The results showed that patients with SYNTAX score > 22 had a higher plasma concentration of NRG-1 than SYNTAX score ≤ 22. Geisberg *et al.* found the negative correlation between NRG-1 levels with CAD's severity, which lower NRG-1 levels related to higher severity. The difference is probably caused by the measurement time of NRG-1

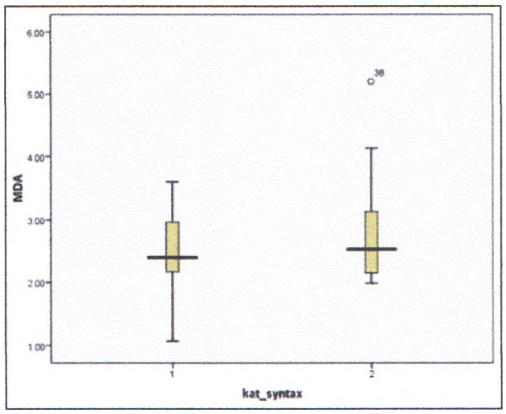

Figure 1: MDA levels and CAD's severity (1 = patients with SYNTAX Score < 22 and 2 = patients with SYNTAX score > 22)

levels [2]. This study measured NRG-1 levels 24 h after primary catheterization, not based on the onset of a heart attack. Then, also, patients who underwent coronary angiography in CAD got initial and continued treatment with cardiac medications in 24 h [11]. Antiplatelet drugs and other cardiac drugs such as aspirin and clopidogrel give an excellent vascular impact. Those lead to endothelial function improvement and may result in increasing NRG-1 expression [5], [12].

Kuramochi et al. found that releasing of NRG is induced by ischemic and reperfusion injuries. Reactive oxygen species induce activation of NRG-1 in myocardial cells [7]. NRG-1 activated during myocardial infarct and cardiomyocytes will proliferate after damage and through the regeneration helped by the intracellular and extracellular signal. NRG-1 regulates cardiogenesis and cardiac regeneration [9], [10].

Vascular endothelial growth factor (VEGF) increased in physiological and pathological state to repair endothelial function. Our study may relate to these conditions, where human endothelial progenitor cells produced together after VEGF in hypoxia and ischemic situations [13]. Thrombosis caused by atherosclerosis leads to hypoxia and released cardiac endothelial cells within hours to restore endothelial walls [14]. Recent studies on rat model myocardial ischemia show peaked of VEGF expression in 3 h after injury, and it can determine the degree of severity of the ischemic injury [15]. Intermittent hypoxia has a cardioprotective effect by regulating VEGF expression in the ischemic rat model [16], [17]. Endothelial function improvement after hypoxia by VEGF leads to an increase of NRG-1 expression [18], [19] [20]. NRG-1 also helped to strengthen the vascular and alleviate cardiac endothelial cells shown in rats' model [21].

MDA levels increase together with CAD's severity. CAD patients with three vessels involved have a significantly higher level of MDA than one vessel involved. However, in this study, MDA levels showed no significant increase in high severity patients. Venkata et al. reported that the MDA plasma levels were significantly higher in inpatient CAD groups compared to the control group ($p<0.05$) [22]. MDA level is a useful marker for the severity of CAD and reflecting the presence of easily removed plaque [23], [24]. MDA can be predictive markers of adverse cardiovascular outcomes [25]. Elevated concentration of MDA relates to severe coronary artery calcification in patients with renal disease [26]. Higher MDA levels mean worse prognosis on CAD who underwent PCI in a recent study [25]. MDA has a stable concentration in blood over 36 h in patients [28].

MDA was produced from lipid peroxidation on oxidative stress. Elevated MDA indicates free radicals production leads to atherogenesis and the development of atherosclerosis caused by coronary heart disease [29], [30]. A recent study shows that smokers' patients got higher oxygen free radical than non-smokers patients [31]. We also found that more than half of our patients were smokers that lead them to produce more MDA. Tobacco and other risk factors play a role in coronary heart disease [31], [32].

Conclusion

Our results suggest that NRG-1 plasma levels do not correlate with CAD severity. However, There was no significant difference between both groups. Patients with SYNTAX score > 22 had a higher plasma concentration of NRG-1 than SYNTAX score ≤ 22. NRG-1 can increase the myocardial angiogenesis, probably through the direct effects of NRG-1 and through the increased expression of VEGF. There was no significant MDA plasma level in patients with moderate high and low severity of CAD. Increased

oxidative stress, such as MDA, was observed in CAD cases and potentially represented a pathogenic factor for atherosclerosis.

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