Conference Paper

The Association Between Serum Resistin Level with the Degree of Coronary Artery Stenosis

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Abstract

Coronary artery stenosis is a thickening of intimal coronary artery due to chronic inflammation of blood vessels, characterized by the accumulation of inflammatory cells, vascular smooth muscle cells, lipid, and fibrotic tissue. Resistin, a cysteine-rich secretory protein, produced by monocytes and adipose cells, increases proinflammatory cytokines. This study was conducted to analyze the association between serum resistin level with the severity of coronary artery stenosis. This cross-sectional study was performed in 60 patients aged 30-70 years old who were suspected to have coronary heart disease (CHD) and underwent coronary angiography at Cardiology Department of Dr. Moewardi Hospital in Surakarta. The cutoff point of serum resistin level was determined by receiver operating curve (ROC). The data were analyzed to determine the prevalence ratio of each variable, followed by logistic regression, $p<0.05$ was considered statistically significant. This study found a significant association between serum resistin level and the severity of coronary artery stenosis. At the cutoff point of 6.37 ng/ml, bivariate and multivariate analysis showed that resistin had the prevalence ratio (PR) of 6.56 (95% CI: 1.705-25.263; p = 0.005) and 7.47 (95% CI: 1.562-35.784; p = 0.012), respectively. Even after adjustment with body mass index, sex, hypertension, dyslipidemia and type 2 DM, resistin showed significant association with the severity of coronary artery stenosis (PR: 7.48; 95% CI: 1.562-35.784; p = 0,012).

Keywords: coronary artery stenosis, resistin.

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1. Introduction

According to the World Health Organization, coronary heart disease (CHD) is the leading cause of mortality, especially in developing countries [1]. The prevalence of CHD in Indonesia has been reported to be 0.5% and keeps escalating since the risks of CHD such as hypertension, dyslipidemia, age, obesity, high saturated fat in the diet and sedentary lifestyle are rocketing as well [2].

Coronary artery stenosis is thickening of intimal coronary artery due to chronic inflammation of blood vessel characterized by the accumulation of inflammatory cells, vascular smooth muscle cells, lipid and connective tissue [3, 4]. Stenosis disturbs myocardial oxygenation and CHD symptoms emerge. Mild coronary artery stenosis of less than 50% arterial lumen does not frequently precipitate clinical symptoms of CHD. Moderate and severe stenosis results clinical symptoms, with stenosis of >50% causes disturbance of coronary artery vasodilatation, while stenosis of >75% causes clinical symptoms such as angina pectoris, acute myocardial infarction and cardiac arrest [5, 6]. The gold standard for diagnosing coronary artery stenosis is coronary angiography, but it is expensive, invasive and requires advance equipment [7, 8].

The ”response to injury” is the most commonly applied theory of atherosclerosis. Endothelial dysfunction due to endothelial injury results in proinflammatory cytokines and adhesion molecules release and vasoconstriction. Proinflammatory cytokines attract monocytes from the vessel which then differentiate into macrophages. Monocyte will release various cytokines leading to chronic inflammation of blood vessels [9, 10]. One of proinflammatory cytokines produced by monocyte is resistin, or “resistin-like molecule” (RELMs) or “Found In Inflammatory Zone” (FIZZ) cytokine, a cysteine-rich secretory protein with molecular weight of 12.5 kDa, produced also by adipocyte stroma. Resistin was expressed on the surface of monocyte. It increases monocyte adhesion to the endothelial cell, lengthen the lifetime of monocyte, stimulate monocyte accumulation on tunica intima of the vessel, enhances vascular smooth muscle cell proliferation, foam cell formation and production of reactive oxygen species [11–13]. Previous studies confirmed that resistin has proatherogenic activity and play an important role in progressive coronary stenosis [14]. This study was conducted to analyze the association between serum resistin level with the severity of coronary artery stenosis.

2. Methods

This cross-sectional study was conducted to analyze the association of serum resistin level to the significance of coronary stenosis. The study subjects were 60 CHD patients hospitalized in June 2017 at cardiology ward of Dr Moewardi Hospital at Surakarta, Central Java, Indonesia. Subjects aged 30-70 years old. We included the patients who underwent angiography for the first time and agreed to be enrolled in the study by signing informed consent. Patients with acute and chronic inflammation characterized by CRP level of >10 mg/dL, history of hyperthyroidism or receiving antithyroid therapy,

hyperglycemic stress and patients receiving dexamethasone or statin therapy for more than 12 weeks were excluded from our study.

Subject's demography and clinical characteristics were retrieved from anamnesis and medical records. Physical examination was performed to complete the clinical information. Simple anthropometric measurements including weight and height to calculate BMI were performed for evaluation of obesity. The significance of coronary stenosis was assessed by coronary angiography and categorized into significant (if luminal narrowing of the coronary artery is $\geq$ 50%) and not-significant (if luminal narrowing of the coronary artery is <50%) [15].

The arterial blood of 4 ml in volume was taken via femoral artery during insertion of the coronary catheter before coronary angiography procedure. The serum was obtained after centrifugation of 3000 rpm for 15 minutes and divided into 2 tubes. Analysis of biochemical parameters performed on these blood samples including serum resistin, C-Reactive Protein, High-Density Lipoprotein-Cholesterol (HDL-C), Low-Density Lipoprotein-Cholesterol (LDL-C), triglyceride and glucose. This analysis was performed by using automatic Advia 1800 chemistry analyzer system. After blood collection, the tubes for measurement of serum resistin were stored immediately at -80°C until analysis. Level of serum resistin was measured by enzyme-linked immune-sorbent assay (ELISA) by using commercial kits: human ResistinELISADEE050 (Demeditec Diagnostic GMBh, Germany). The study was approved by the local ethics committee and informed consent was obtained from all subjects.

Data were tested for normal distribution using the Kolmogorov–Smirnov test. Data were expressed as mean $\pm$ SD or median and percentile 25^{th}—75^{th} in accordance to their distribution. Categorical data were presented as frequency and percentage. Variables normally distributed were compared by unpaired Student's t-test. Variables not normally distributed were compared by Mann-Whitney U-test. Serum resistin cutoff was calculated with the ROC curve. Diagnostic sensitivity and specificity for serum resistin level were calculated using a 2x2 table. To find out the association between serum resistin and the significance of coronary stenosis, we used bivariate and multivariate analysis with logistic regression to control other variables affecting the significance of stenosis such as sex, body mass index (obesity if BMI $\geq$25), history of hypertension, history of type 2 diabetes mellitus and history of dyslipidemia. The analysis was performed by SPSS statistical software package program version 23, p-value < 0.05 was considered significant.

3. Results

Demographic and biochemistry characteristics of the subjects have been summarized in Table 1. The mean age of subjects was 58.3±9.2 years old, 71.7% were male and the incidence of significant coronary stenosis was 78.3%. Amongst demographic variables, history of hypertension were the only significant variables differ between non-significant and significant coronary stenosis (p=0.041). Serum resistin level also differs significantly between the two groups (p=0.008).

The cutoff value for serum resistin level was calculated using the ROC curve. Diagnostic sensitivity and specificity for serum resistin level were calculated using a 2x2 table. At the cut off value of 6.37 ng/mL serum, resistin has an area under the curve (AUC) of 0.707 (95%CI: 0.543-0.870; p=0.028) with sensitivity and specificity for coronary stenosis were 64.6% and 75%, respectively. This resistin cutoff then is used in the further analyses.

Bivariate analysis demonstrated an association between serum resistin level and significant coronary stenosis with the prevalence ratio (PR) of 6.56 (95%C I: 1.71-25.26; p=0.005). Hypertension also associated with the significance stenosis with PR of 3.82 (95%CI: 1.06-13.77; p=0.041) (Table 2).

The result of logistic regression multivariate analysis between serum resistin level and other variables affecting the significance of coronary stenosis was demonstrated in Table 3. After adjustment for history of hypertension (model 1), serum resistin level revealed the association with significant coronary stenosis with the PR 5.69 (95%CI 1.43-22.67; p=0.014). In all models, even after adjustment for history of hypertension, history of dyslipidemia, BMI, sex and history of type 2 DM, serum resistin level of ≥ 6.37 ng/ml still demonstrated an association with significant coronary stenosis. History of hypertension also showed an association with significant coronary stenosis after adjustment for history of dyslipidemia, BMI, sex, and history of type 2 DM. History of dyslipidemia, BMI, sex, and history of type 2 DM had no association with significant coronary stenosis.

4. Discussion

The present study evaluated the association between the serum resistin level with the significance of coronary stenosis. In significant coronary artery stenosis (luminal narrowing of the coronary artery is ≥ 50%), coronary artery wall losses its ability to vasodilate, then myocardial oxygenation disturbed. If the coronary stenosis is severe (>75%), clinical symptoms will occur [5, 6]. In this study, significant stenosis occurred in 78.3% of subjects.

Table 1: Demographic and biochemistry characteristics of the subjects.

	Total	Coronary stenosis		p
	n=60 (100%)	Not-significant	Significant	
		[n= 13 (21.7%)]	[n=47 (78.3%)]	
Sex (%)[a]				
Male	43 (71.7%)	10 (76.9%)	33 (70.2%)	0.461
Female	17 (28.3%)	3 (23.1%)	14 (29.8%)	
Age (year)[b]	58.3 ± 9,2	53.90 ± 9.02	59.56 ± 8.94	0.05
BMI (kg/m^2)*b*	23.61 ± 2.93	23.04 ± 2.61	23.76 ± 3.03	0.44
BMI category (%)				
Normal	42 (70%)	9 (69.2%)	33 (70.2%)	0.597
Obesity	18 (30%)	4 (30.8%)	14 (29.8%)	
BP systolic (mmHg)[b]	141.6 ± 28.56	136.92 ± 30.72	142.87 ± 28.14	0.511
BP diastolic (mmHg)[b]	85.0 ± 15.18	83.08 ± 15.57	85.53 ± 15.51	0.61
History of hypertension (%)[a]				
No	18 (30%)	7 (53.8%)	11 (23.4%)	0.041*
Yes	42 (70%)	6 (46.2%)	36 (76.6%)	
History of type 2 DM (%)[a]				
No	39 (65%)	8 (61.5%)	31 (66%)	0.505
Yes	21 (35%)	5 (38.5%)	16 (34%)	
History of dyslipidemia (%)[a]				
No	24 (40%)	5 (38.5%)	19 (40.0%)	0.58
Yes	36 (60%)	8 (61.5%)	28 (59.6%)	
NFBG (mg/dl)[c]	128.3 (100.2-133.75)	121.85 (114-132.5)	130.09 (99 – 134)	0.607
LDL-C (mg/dl)[b]	120.55 ± 36.76	123.08 ± 28.81	119.85 ± 38.92	0.782
HDL-C (mg/dl)[b]	38.87 ± 9.8	42.38 ± 6.69	37.89 ± 10.35	0.145
Triglyceride (mg/dl)[b]	141.52 ± 69.98	174.15± 81.05	132.49 ± 64.68	0.057
Serum resistin level (ng/mL)[c]	7.92 (5.68 – 8.63)	6.02 (5.07 – 7.64)	8.39 (5.94 – 8.9)	0.008*

BP bloodpressure.

NFBG non-fastingbloodglucose.

LDL-C low-density lipoprotein cholesterol.

HDL-C high-density lipoprotein cholesterol.

[a] categorical data.

[b] datanormallydistributed.

[c] data not normallydistributed.

*p significant if <0.05.

The median and percentile 25^{th}—75^{th} of resistin level differ significantly between significant and not-significant stenosis group [8.39 (5.94 – 8.9) vs 6.02 (5.07 – 7.64),

Table 2: Bivariate analysis of serum resistin level and other variables affecting the significance of coronary stenosis.

Variable	Coronary stenosis		PR (95%CI)	p
	Not-significant	Significant		
Serum resistin level(ng/mL)				
< 6.37	9	12	6.56 (1.71-25.26)	0.005*
≥ 6.37	4	35		
Sex				
Male	10	33	0.77 (0.17-2.97)	0.461
Female	3	14		
BMI category				
Normal	9	33	0.95 (0.25- 3.62)	0.597
Obesity	4	14		
History of hypertension				
No	7	11	3.82 (1.06-13.77)	0.041*
Yes	6	36		
History of type 2 DM				
No	8	31	0.83 (0.23- 2.94)	0.505
Yes	5	16		
History of dyslipidemia				
No	5	19	0.92 (0.26-3.25)	0.58
Yes	8	28		
*p value is significant if <0.05				

p=0.008). Bivariate analysis showed that a serum resistin level of ≥ 6.37 ng/mL is significantly associated with the degree of coronary stenosis. Pathophysiologically, coronary stenosis caused by atherosclerosis is a sustained chronic inflammation. The more severe the stenosis, the atherosclerotic lesion is thicker. More monocytes will differentiate into macrophage, then accumulate inside the coronary intima, leading to more resistin released into circulation [14]. This finding is similar to those reported by Krecki *et al* [16] and Ohmori *et al* [17] but it is contradictory from that of Mortavazi *et al*'s study [18].

Bivariate analysis also revealed a significant association between histories of hypertension with the significance of coronary stenosis. Ohmori *et al* [17] and Kelley *et al* [19] suggested that a history of hypertension was significantly associated with the degree of coronary stenosis, which is similar to our study. Angiotensin II will cause vasoconstriction, aldosterone secretion, vascular smooth muscle cell proliferation, fibrosis, superoxide formation, inflammation, and thrombosis, resulting in endothelial dysfunction. Hypertension results in coronary artery wall spasm so that vasodilatation decreases and coronary luminal narrows [10].

TABLE 3: Multivariate analysis of serum resistin level andother variables affecting the significance of coronary stenosis.

Variable	PR	95%CI	p
Model 1			
Serum resistin≥ 6.37 ng/mL	5.69	1.43-22.67	0.014*
History of hypertension	3.04	0.77-12.03	0.114
Model 2			
Serum resistin≥ 6.37 ng/mL	6.73	1.58-28.61	0.010*
History of hypertension	4.49	0.94-21.35	0.059
History of dyslipidemia	0.35	0.07-1.75	0.2
Model 3			
Serum resistin ≥ 6.37 ng/mL	6.99	1.62-30.18	0.009*
History of hypertension	4.61	0.98-21.85	0.054
History of dyslipidemia	0.36	0.07-1.83	0.221
BMI	0.67	0.14-3.10	0.609
Model 4			
Serum resistin ≥ 6.37 ng/mL	7.72	1.63-36.35	0.010*
History of hypertension	4.71	1.01-22.14	0.049*
History of dyslipidemia	0.33	0.06-1.76	0.197
BMI	0.65	0.14-3.03	0.582
Sex	1.44	0.26-7.87	0.676
Model 5			
Serum resistin ≥ 6.37 ng/mL	7.48	1.56-35.78	0.012*
History of hypertension	5.01	1.02-24.66	0.047*
History of dyslipidemia	0.31	0.05-1.77	0.186
BMI	0.66	0.14-3.11	0.602
Sex	1.41	0.26-7.76	0.696
Historyoftype 2 DM	0.74	0.16-3.45	0.707
*p significant if <0.05.			

Based on our finding, BMI has no significant association with coronary stenosis. This confirms the study conducted by Rossi *et al* [20] but differs from de Leon *et al*'s study [12]. Body mass index cannot be used to measure body fat directly and it does not denote body fat distribution. Fat distribution is the more significant variable for cardiovascular risk, insulin resistance, type 2 DM, atherosclerosis and other diseases compared to BMI and waist circumference is a representation of the body fat distribution [21].

History of diabetes is not associated with significant stenosis. Glycemic control plays a more important role in the pathophysiology of atherosclerosis and coronary stenosis than random or fasting blood glucose. The accumulation of advanced glycation end products (AGEs) affects arterial wall more, which will induce proinflammatory cytokines

release. Chronic hyperglycemia is a trigger for the occurrence of oxidative stress which promotes atherosclerosis [22].

In our study, history of dyslipidemia was not associated with significant stenosis. This might have resulted from statin therapy given to our subjects with dyslipidemia. Patients undergoing statin therapy were included in this study only when they used statin for less than 12 weeks. The use of statin will influence HDL-C, LDL-C and triglyceride level. This possibly results in no significant association between dyslipidemia and the degree of coronary stenosis.

In multivariate analysis, after adjustment with history of hypertension, history of dyslipidemia, BMI, sex and history of type 2 DM, serum resistin level of ≥ 6.37 ng/ml still demonstrated a significant association with the coronary stenosis. History of hypertension also showed an association with the significance of coronary stenosis after adjustment on a history of dyslipidemia, BMI, sex, and history of type 2 DM.

Our study had several limitations, including relatively small sample size, only 60 subjects were enrolled in our study. Moreover, it was a cross-sectional design and did not prove causation. A further study with case-control design was needed to obtain the odds ratio in order to clarify this relationship. It is also necessary to give a closed control on variable type 2 DM and dyslipidemia.

5. Conclusion

Serum resistin level is associated with the significance of coronary stenosis, even after adjustment of other factors affecting the degree of coronary stenosis. Resistin cutoff point of ≥6.37 ng/ml has a prevalence ratio of 6.56 (95% CI: 1.71-25.26) for more severe coronary stenosis.

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