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Correlation between Carotid Intimal-Media Thickness and Coronary Artery Disease Severity in Stable Coronary Artery Disease Patients

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ABSTRACT

Background: Atherosclerosis is a fundamental process in the natural course of coronary heart disease (CHD), carotid artery disease and peripheral artery disease. Atherosclerosis is caused by an imbalance of homeostasis in the level of the endothelial layer and the presence of risk factors. The manifestations of coronary atherosclerosis have a wide spectrum of diseases, ranging from subclinical to clinical phases. In patients without CHD symptoms, changes in carotid artery morphology include carotid intimal-media thickness (CIMT) and carotid plaques which correlated with CHD. This study aims to see the relationship between CIMT with the severity of coronary lesions in stable coronary artery disease.
Methods: The study was an analytical observational research using cross sectional design. Data was taken by consecutive sampling from outpatient hospital clinic. The CIMT score was obtained from the examination of a communis carotid artery using a B-mode ultrasound device. The value of CIMT is divided into 2 groups based on the value of the sensitivity curve and the specificity curve. The value of Syntax was obtained from the catheterization laboratory and the factors that influenced it were recorded. Pearson correlation test is used to analyze the relationship of CIMT and Syntax value. The logistic regression test used for multivariate test.
Results: Of the 58 patients, there were 33 subjects who had a CIMT score of > 0.71 mm and 25 subjects who had a CIMT score of ≤0.71 mm. There is a positive correlation ($r = 0.403$; $p < 0.05$) between CIMT value and Syntax value. Subjects who have high Syntax value in the group with a CIMT value >0.71 mm compared to CIMT values ≤0.71 mm were 29 versus 4 (RR: 1.831; CI 95%: 1.194-2.807; $p = 0.01$). A multivariate test showed CIMT consistently as a independent risk factor of Syntax value in stable coronary artery disease with RP 5.27 (CI 95%: 1.306-25.047; $p = 0.021$).
Conclusion: The increase in CIMT value has a significant positive correlation with the Syntax value. A CIMT > 0.71 mm is a independent risk factor of high Syntax value in stable coronary artery disease with prevalence ratio 5.27.

Keywords: CIMT; Syntax value; stable CAD

INTISARI

Latar Belakang: Aterosklerosis merupakan proses fundamental dalam perjalanan alamiah penyakit jantung koroner (PJK), penyakit arteri karotis dan penyakit arteri perifer. Aterosklerosis disebabkan oleh ketidak seimbangan homeostasis pada level lapisan endotel dan adanya faktor risiko. Manifestasi aterosklerosis koroner berspektrum luas, dari fase subklinis sampai dengan klinis. Pada pasien tanpa gejala PJK, perubahan morfologi arteri karotis meliputi penebalan intima-media karotis (PIMK) dan plak karotis yang berkorelasi dengan PJK. Penelitian ini bertujuan menyelidiki hubungan antara PIMK dengan keparahan lesi koroner pada penyakit arteri koroner stabil.

Metode: Penelitian ini merupakan penelitian observasi analisik dengan disain potong lintang. Data diambil dengan sampel berurutan dari pasien di poliklinik. Skor PIMK didapatkan dari pemeriksaan arteri karotis komunis menggunakan alat ultrasonografi B-mode. Nilai PIMK dibagi dua grup berdasarkan nilai kurva sensitivitas dan spesifitas. Nilai Syntax didapatkan dari hasil laboratorium kateterisasi dan faktor-faktor yang mempengaruhi didokumentasi. Tes korelasi Pearson digunakan untuk menganalisis hubungan nilai PIMK dan Syntax. Tes regresi logistik digunakan untuk uji multivariat.
Hasil: Dari 58 pasien, terdapat 33 subjek dengan skor PIMK > 0,71 mm dan 25 subjek dengan PIMK skor ≤ 0,71 mm. Terdapat korelasi yang positif (r = 0,403; p <0,05) antaran nilai PIMK dan Syntax. Subjek yang mempunyai nilai Syntax tinggi pada kelompok PIMK > 0,71 mm lebih banyak dibanding pada kelompok PIMK ≤ 0,71 mm, yaitu 29 dibanding 4 subjek, RR: 1.831; CI 95%: 1.194-2.807; p = 0.01. Uji multivariat menunjukkan PIMK secara konsisten merupakan faktor risiko independen nilai Syntax pada penyakit arteri koroner stabil dengan PR 5,27 (95% KI: 1,306-25,047; p = 0,021).
Simpulan: Peningkatan nilai PIMK berhubungan positif dan bermakna dengan nilai Syntax. Nilai PIMK > 0.71 mm merupakan faktor risiko independen nilai Syntax tinggi pada penyakit arteri koroner stabil dengan rasio prevalensi 5,27.

INTRODUCTION

Atherosclerosis is the most common cause of coronary heart disease (CHD), carotid artery disease (CAD) and peripheral arterial disease (PAD). Atherosclerosis itself is not a fatal disease but the process of thrombosis which is the process of rupture of atherosclerosis plaque is the cause of serious events such as acute coronary syndrome and stroke.[1] Atherosclerosis is a fundamental process in the natural course of CHD. The manifestations of coronary atherosclerosis have a wide spectrum of diseases, ranging from subclinical to clinical phases.[2]

In patients without CHD symptoms, changes in carotid artery morphology include carotid intimal-media thickness (CIMT) and carotid plaques were correlated with CHD.[2] The relationship between CIMT and risk of cardiovascular events has been extensively studied in large studies and it is expected that asymptomatic plaque can be used for predict future cardiovascular events.[3] In addition to predicting a subclinical process, CIMT examination is also common in monitoring the progression of the disease and treatment due to good reproductive rates.

In the Atherosclerosis Risk in Commmunities study (1993) revealed that CIMT has a limited value that varies by race, gender and age.[5] Rilantoro and Fadilah (1999) examined the association of CIMT with the severity of coronary lesions (grouping according to the number of blood vessels) in the diabetes mellitus population (DM) but no statistically significant relationship.[6] The relationship of CIMT degree to the severity of coronary lesions (Syntax system) has not been studied in Indonesia therefore this study aims to look at the relationship between CIMT and the severity of coronary lesions (Syntax system) in the stable coronary artery disease (SCAD) population.

METHODS

The design of this study was a cross sectional study, which assessed the relationship between the CIMT value and the severity of coronary lesions in SCAD populations with positive treadmill test (TMT) results or significant lesions results on multi-slice computed tomography (MSCT) examination at Dr. Sardjito Hospital, Yogyakarta, Indonesia from May 2017 to August 2017.

The independent variables in this study were the thickness of communis carotid intimal-media while the dependent variable on this study was the severity of the coronary lesions, both

of which were taken during hospitalization. The confounding variables include age, sex, blood pressure, diabetes mellitus, history of smoking and dyslipidemia.

In this study the inclusion criteria of the study subjects were as follows: (1) male or female patients with suspected SCAD from positive TMT or coronary MSCT with significant lesions, (2) sinus rhythm on ECG recordings, (3) age 18-75 years, and (4) neck examination area can be well visualized. The exclusion criteria were patients with a history of myocardial infarction, history of ischemic stroke and suffering from chronic renal failure.

The patients were performed coronary angiography and ultrasound CIMT, after being detected as SCAD based on positive TMT or coronary MSCT with significant lesions. All TMT and MSCT results as well as coronary angiography and ultrasound CIMT were well listed in the medical record. The standard difference of examination is minimized by performing a suitability analysis between the two CIMT examiners and the severity of the coronary lesions using a kappa.

The data were analyzed using SPSS for Windows software version 22.0. The basic characteristics were displayed as a mean or percentages. Categorical variables were compared using Chi Squared (X^2) test. The relationship between CIMT value and Syntax value were tested by Pearson correlation test. The numerical variables in the CIMT group and the severity parameters of the coronary lesions were analyzed for their correlations using the independent sample T Test or Mann Whitney Test based on the normality of the data distribution. Confounding variables were analyzed using multivariate analysis with logistic regression test. The p value <0.05 was considered statistically significant.

This study used the approval of the ethics committee of Faculty of Medicine, University of Gadjah Mada Yogyakarta and permission from the Dr. Sardjito Hospital, Yogyakarta, Indonesia.

RESULT

This study took place from May 2017 to August 2017 at Dr. Sardjito Hospital, Yogyakarta, Indonesia. During this study period, as many as 302 patients with suspected SCAD underwent TMT and coronary MSCT. Total subjects met the inclusion criteria were 152 (figure 1). As many as 94 subjects were excluded because of a history of ischemic stroke, history of myocardial infarction and chronic heart failure. Therefore, 58 subjects were enrolled in the study, consisting of men as many as 50 subjects (86%) and women as many as 8 subjects (14%). The mean age of the subjects was 56.96 ± 7.73 years, with the highest risk factors being hypertension 39 subjects (67.2%), smoking 35 subjects (60.3%), dyslipidemia 33 subjects (56.9%), diabetes mellitus 18 subjects (31%) and family history of 9 subjects (15.5%) (table 1).

The calculation of correlation between CIMT and Syntax values with Pearson test showed a positive relationship with r = 0.403 (p <0.05) (figure 2).

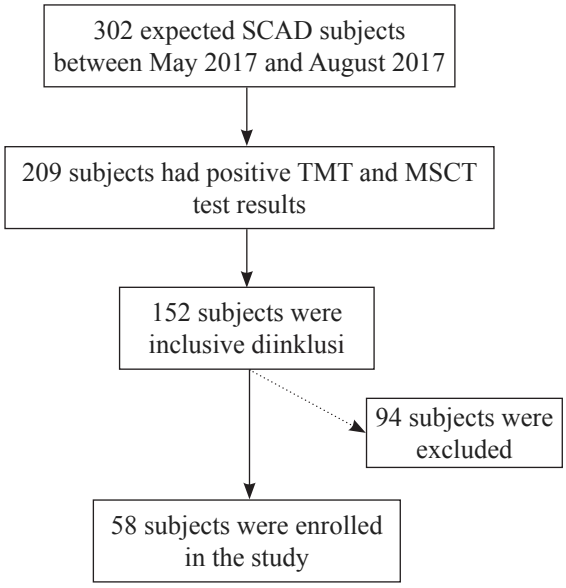

Figure 1. The number of research subjects.

Table 1. The subject baseline characteristics

Variables	Value (n=58)
Sex	
Male; n(%)	50 (86.2%)
Female; n(%)	8 (13.8%)
Age (years)*	56.96±7.73
Risk factor	
Hypertension; n(%)	39 (67.2%)
Diabetes mellitus; n(%)	18 (31%)
Dyslipidemia; n(%)	33 (56.9%)
Smoking; n(%)	35 (65.3%)
Familial history; n(%)	9 (15.5%)
Systolic blood pressure (mmHg)**	127.5 (76-190)
Body mass index (kg/m^2)*	25.85±3.37
Lipid profile	
Cholesterol (mg/dl)**	148 (85-246)
LDL cholesterol (mg/dl)*	96.31±32.27
HDL cholesterol(mg/dl)**	40.0 (35-174)
Trygliserida (mg/dl)**	125.5 (39-287)
CIMT value	
Thick (>0.71 mm); n (%)	33 (56.9%)
Thin (≤0.71 mm); n (%)	25 (43.1%)
Syntax score	
High; n(%)	41 (70.7%)
Low; n(%)	17 (29.3%)

* normal data distribution, shown in the mean and standard deviation
** abnormal data distribution, shown in median

The analysis with the receiver operating charateristic (ROC) curve shows the value of the area under the curve of 74% (95% I: 95% -89%; p = 0.003). On the sensitivity and specificity curve the CIMT value of 0.71 mm was obtained with sensitivity of 70% and 76% specificity to predict high Syntax value.

The basic characteristics of research subjects based on CIMT grouping were differentiated into thin CIMT (≤0.71 mm) and thick CIMT (> 0.71 mm), according on ROC curve. Description of the characteristics of both groups included the demographic characteristics and clinical characteristics. Demographic characteristics included age and sex, while clinical characteristics included blood pressure, risk factors, body mass index (BMI) and laboratory data (lipid profile). Statistically the age

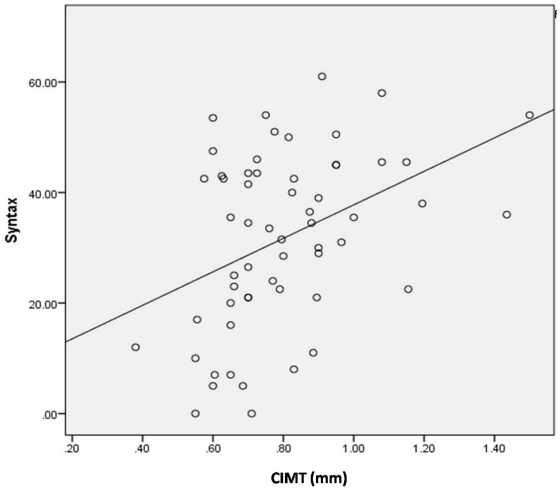

Figure 2. A scatter-plot shows positive correlation between CIMT and Syntax (r = 0.403; p <0.05).

and number of blood vessels had a significant difference between the two groups (Table 2).

During the study, subjects who had a high Syntax value were 41 out of 58 subjects (70%). The significantly different variables between groups with low Syntax values and those with high Syntax values included age, hypertension and DM, while the other variables did not differ significantly between the two groups (Table 3).

Multivariate analysis was performed on variables that could potentially be a confounding factor with a value of p <0.25 in the univariate analysis. Multivariate analysis in this study included variables of hypertension, diabetes mellitus, age and systolic pressure. Based on multivariate analysis, CIMT remained associated with Syntax values compared to other variables (PR 5.27, 95% CI: 1.306-25.047; p = 0.021) (Table 4).

DISCUSSION

The mean age of the subjects of this study was 56.49 ±7.15 years. Similar results were found in the Ikeda et al. (2012) study of 56.9 ± 10.9 years.[7] The age is an unmodified cardiovascular risk factor. The incidence of cardiovascular disease significantly increased

Table 2. Comparison of the basic characteristics of the CIMT group >0.71 mm and CIMT ≤0.71 mm in stable CHD patients

Variables	CIMT >0.71 mm (n=33)	CIMT ≤0.71 mm (n=25)	P value
Sex			
Male; n(%)	29(87.9)	21(84.0)	0.671
Female; n(%)	4(12.1)	4(16.0)	
Age (years)*	59.7 ± 6.13	53.28±8.17	0.001
Risk factor			
Hypertension; n(%)	24 (72.7)	15 (60.0)	0.306
Diabetes mellitus; n(%)	13 (39.4)	5 (20.0)	0.114
Dyslipidemia; n(%)	20 (60.6)	13 (52.0)	0.512
Smoker; n(%)	13 (39.4)	10 (40.0)	0.784
Family history; n(%)	5 (15.2)	4 (16.0)	0.930
Systolic pressure (mmHg)**	140 (76-190)	125 (96-180)	0.078
BMI (kg/m^2)*	25.78 ± 3.45	25.95 ± 3.34	0.846
Lipid profile			
Cholesterol (mg/dl)**	160 (85-242)	138 (107-246)	0.593
LDL cholesterol (mg/dl)*	97.6 ± 29.5	94.6 ± 36.1	0.735
HDL cholesterol (mg/dl)**	40 (20-51)	41 (10-122)	0.514
Triglyceride (mg/dl)**	130 (39-243)	118 (63-287)	0.765
Involvement of coronary arteries			
Normal; n (%)	0 (0)	2 (8.0)	<0.001
1 VD; n (%)	0 (0)	9 (36.0)	
2 VD; n (%)	16 (48.5)	6 (24.0)	
3 VD; n (%)	17 (51.5)	8 (32.0)	
Syntax value			
High; n(%)	29 (87.9)	12(48.0)	0.001
Low; n(%)	4(12.1)	13 (52.0)	

CIMT is carotid intima media thickness; BMI is the body mass index; LDL is low density lipoprotein; HDL is high density lipoprotein.
*distribution of normal data, shown in mean and standard deviation and analyzed with unpaired T test.
**abnormal data distribution, shown in median and analyzed by Mann-Whitney test.

at age above 55 years. The mean age of the CIMT group > 0.71 mm in this study was 59.7 ± 6.13 years higher than the mean age of CIMT ≤0.71 mm group which was 53.28 ± 8.17 years (p = 0.001). In a previous study there was an indication that increasing age there was an increase in the value of CIMT and plaque scores in the European population.[8]

Subjects with a CIMT thin (score of ≤0.71 mm) tended to have normal coronary artery pattern, otherwise CIMT thick (>0.71 mm) had a vascular number lesion ≥2. Nevertheless in this study there were 8 subjects (13%) had lesions involved 3 blood vessels but the value of CIMT was low. This result is consistent with research conducted by Kablak-Ziembicka et al. (2004).[9] This study showed that the increase in the number of coronary blood vessels involved was associated with increased CIMT values, subclavian artery stenosis and vertebral artery and low CIMT value inconsistency with the degree of severity coronary in a small population because of low sensitivity and specificity.[9]

Different variables were significant between the high Syntax group and low Syntax groups including age and hypertension. The mean age in the high Syntax group had a higher value than the low Syntax group (p = 0.025). Age

Table 3. Comparison of the basic characteristics of the high Syntax group and low Syntax group in stable CHD patients

Variables	High Syntax (n=41)	Low Syntax (n=17)	p
Sex			
Male; n(%)	36 (87.8)	14 (82.4)	0.584
Female; n(%)	5 (12.2)	3 (17.6)	
Age (years)*	58.41±6.28	53.47±9.81	0.025
Risk factor			
Hypertension; n(%)	31 (75.6)	8 (47.1)	0.035
Diabetes mellitus; n(%)	15 (36.6)	3 (17.6)	0.156
Dyslipidemia; n(%)	24 (58.5)	9 (52.9)	0.695
Smoker; n(%)	25 (60.9)	10 (58.8)	0.988
Familial history; n(%)	7 (12%)	2 (3%)	0.611
Systolic pressure (mmHg)**	133 (76-190)	120 (99-180)	0.185
BMI (kg/m^2)*	25.71±3.54	26.20±3.00	0.621
Lipid profile			
Cholesterol (mg/dl)**	155 (85-242)	138 (101-246)	0.412
LDL cholesterol (mg/dl)*	96.97±31.65	94.70±34.68	0.810
HDL cholesterol (mg/dl)**	40 (29-90)	41 (28-122)	0.758
Triglyceride (mg/dl)**	130 (39-287)	118 (85-244)	0.858
CIMT			
Thick (>0.71 mm); n(%)	29 (70.7)	4 (23.5)	0.001
Thin (≤0.71 mm); n(%)	12 (29.3)	13 (76.5)	

CIMT is carotid intima media thickness; BMI is the body mass index; LDL is low density lipoprotein; HDL is high density lipoprotein.
*distribution of normal data, shown in mean and standard deviation and analyzed with unpaired T test.
**abnormal data distribution, shown in median and analyzed by Mann-Whitney test.

Table 4. Multivariate analysis of several variables that affect the value of Syntax

Variable	PR	CI 95%	p
CIMT thick (>0.71 mm)	5.27	1.306-25.047	0.021
Hypertension	4.89	0.939-25.472	0.059
Diabetes mellitus	2.18	0.393-12.149	0.372
Age	0.96	0.865-1.061	0.411
Systolic pressure	1.01	0.973-1.043	0.675

has a significant correlation to the severity of coronary lesions.[10] Mechanisms that contribute to accelerated atherosclerosis as age increases include increased fibrinogen, coagulation factor changes (V, VIII, IX and XIIa), von-Willebrand factor and increased plasminogen activator inhibitor that may inhibit fibrinolysis process. Moreover platelet activity increases in terms of attachment to arterial walls in older populations than younger ones.[11]

The most risk factors in this study were hypertension, smoking, dyslipidemia and diabetes mellitus. Hypertension has a significantly different value in the High Syntax group when compared to the lower Syntax group. Coronary angiographic features show more complex, calcified and discreet lesions in stable CHD patients with hypertension as compared to stable CHD without hypertension.[12] In this study, hypertension ranks at the top. The high percentage of hypertension in this study cannot be determined clearly the reason.

In this study, risk factors such as dyslipidemia, smoking, family history and BMI

did not differ significantly between high and low Syntax groups. This is similar to a study by Nicholls et al. (2006) in 654 patients showing that traditional risk factors except diabetes mellitus were not associated with atherosclerotic plaque levels measured by intravascular ultrasonography.[14] In some previous studies, diabetes mellitus was an independent risk factor for the severity of coronary lesions.[15,16] However, it is not found in this study. This may be due to the limited number of research subjects so it is not strong enough to see the difference in proportions and risk factors.

CONCLUSION

There was a positive correlation relationship between CIMT value and Syntax value in stable CAD patient. The CIMT value >0.71 mm was an independent risk factor of high Syntax value stable CAD patient with prevalence ratio 5.27.

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