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Atherosclerosis Prediction with High Sensitivity C-Reactive Protein (hs-CRP) and Related Risk Factor in Patient with Dyslipidemia

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Abstract

BACKGROUND: Inflammation plays a major role in the initiation, destabilization and the progression of atherosclerosis. High Sensitivity C-Reactive Protein (hs-CRP) reflects active systemic inflammation and have shown to be a strong predictor of future cardiovascular events.

AIM: The purpose of this study was to determine the role of High Sensitivity C-Reactive Protein (hs-CRP) independent for atherosclerosis severity prediction and to find out which factors largely is affecting hs-CRP level in dyslipidemia patient.

METHODS: A total of 388 patients (267 dyslipidemia, 121 controls) were enrolled in this study. We investigated whether plasma hs-CRP is associated with atherosclerosis severity that was quantified by *ankle-brachial index* (ABI) and Doppler ultrasound. Related risk factor that influence hs-CRP levels in patients with dyslipidemia included determination of age, gender, diabetes, smoking, hypertension, total cholesterol, TG, LDL, HDL, and fasting glucose.

RESULTS: Data showed a significant association between hs-CRP concentration level and the severity of atherosclerosis ($p < 0.01$). Univariate analysis showed that fasting plasma glucose, triglyceride, and BMI were significantly positively correlated with hs-CRP levels. Whereas, HDL cholesterol was negatively correlated with hs-CRP levels. Multivariate regression analysis using model 1 and 2, showed that in determining hs-CRP levels, triglyceride and BMI were taking a big role.

CONCLUSION: Hs-CRP correlates with extent of atherosclerosis, and high triglyceride and BMI is closely associated with high hs-CRP levels in patients with dyslipidemia.

Introduction

Recent study has provided strong evidence for the importance of primary or secondary inflammatory processes in the pathogenesis of atherosclerosis [1], [2]. C-reactive protein, as a marker of chronic inflammation have been found in patients with peripheral arterial disease, this can be interpreted as a systemic reaction to inflammatory processes in the vessel wall [3], [4]. The mechanism of inflammation plays a central role in all phases of atherosclerosis, from the initial recruitment of circulating leukocytes to the arterial wall until the rupture of the plaque.

High Sensitive C-Reactive Protein (hs-CRP) has long been studied as one of the inflammatory biomakers with high sensitivity in several diseases, especially those related to CHD [2], [3]. Hs-CRP level has been reported being associated with carotid atherosclerosis in patients with type 2 diabetes mellitus [5], [6], and has been suggested being a

useful marker to predict an accelerated atherosclerotic process. There for we investigate the possible association between serum hs-CRP with atherosclerosis severity. hs-CRP levels were also shown associated with increased cardiovascular risk [7], [8], [9], [10]. Several new pharmacological approaches have been discovered to reduce hs-CRP levels [11], [12]. We examined about the accumulation of several atherosclerosis related risk factors influenced serum hs-CRP levels and tested in patients with dyslipidemia to assess which factor that took a big role in influencing hs-CRP levels.

Material and Methods

The study was carried out in a cross-sectional manner, with purposive sampling. We enrolled 267 sample patients with dylipidemia in line with inclusion criteria and exclusion criteria in the present study who visited Sanjiwani Hospital Gianyar on January-June 2018. The control group consisted 121 patients matched the aged and without dyslipidemia diagnosis. Traditional risk factors used in multivariable analyses included: age, gender, diabetes, smoking, hypertention, total cholesterol, TG, LDL, HDL, and fasting glucose. We excluded patients with the following diseases: autoimmune disease, acute inflammatory disease, malignancy, severe liver dysfunction, severe renal dysfunction (male: creatinine Cre ≥ 1.2 mg/dL; female: Cre ≥ 1.0 mg/dL), severe hypertriglyceridemia (triglyceride [TG] ≥ 400 mg/dL), using steroid and/or immunosuppressive agents, and pregnant patients. The Faculty of Medicine Udayana University ethics committee approved the study protocol (No. 34 / UN14.16 / 2018), and informed consent was obtained from each patient by showing it and with a full explanation of the study.

Determination of Atherosclerosis severity.

Vascular Doppler MD2 Hungleight with an 8MHz transducer and a random-zero sphygmomanometer with the cuff positioned just proximal to the elbow/malleoli was used to measure of ankle-brachial index (ABI) and In Doppler Ultrasound each lesion was visually estimated for percent diameter stenosis rounded to the nearest 10%. No atheroscleoris: ABI > 0.9 and stenosis < 10%, Mild to moderate atherosclerosis: ABI 0.7-0.9 and stenosis (10% to 60%), severe atherosclerosis ABI < 0.7 and stenosis (70% to 100%).

Laboratory Analysis

C-reactive protein was measured by an enzyme immunoassay (Abbott Diagnostics, Abbott Park, Illinois), the detection limit of the assay was 0.2 mg/liter. For clinical practice, a threshold level of 5.0 mg/liter is recommended. Serum concentration of trygliceride, glucose and cholesterol ware measure using an autoanalyzer (Hitachi/Boehringer Mannheim, Germany)

Statistical Analysis

The Mann – Whitney U-test was used to compare two groups. The Kruskal–Wallis test was used to carry out overall group comparisons, and the Steel – Dwass test was used to carry out between-group comparisons. Spearman's rank correlation was carried out to study the correlation between hs-CRP levels and clinical parameters. Multivariate regression method was used to analyze the factors independently contributing to serum hs-CRP levels. All data will analyses performed using SPSS for Windows, version 20.00 (SPSS Inc., Chicago, Illinois) with significance (*P < 0.05, **P < 0.01).

Results

A total of 388 subjects were enrolled this study that devided to controls and patients' group. The main clinical and laboratory findings of patients and control are shown in Table 1. The mean age of patiens was about 8 years hinger than controls. In the patient's groups, there were fewer female, but more male, smokers, diabetes, hypertension, and high level of hs- CRP.

Table 1: Baseline Characteristics of Patients and Controls

	Controls		Patients	
	Mean ± SD	90%-range	Mean ± SD	90%-range
Age (years)	42.5 ± 7.8	32.7-62.7	56.2 ± 9.1	39.4-70
BMI	25.7 ± 4.0	20.8-33.4	26.8 ± 3.7	21.1-3.33
Smokers (%)	22	-	51	-
Diabetes (%)	6	-	21	-
Hypertension (%)	33	-	57	-
Male (%)	56	-	63	-
Female (%)	44	-	37	-
Total cholesterol (mg/dl)	160 ± 23.2	150.2-190.4	240 ± 43	174-317
LDL	70 ± 26.7	60.9-100.6	170 ± 38	112-237
Cholesterol (mg/dl)				
Triglyceride (mg/dl)	120 ± 13.2	100.2-150.4	150 ± 45	105-195
HDL	45 ± 10.6	30.7-60	44.1 ± 12.0	27.0 – 66.5
Cholesterol (mg/dl)				
Fasting plasma glucose	100.6 ± 8.9	90.5-102	120 ± 18	102-138
Hs-CRP (μg/ml)	0.87 ± 1.34	0.00-3.65	1.46 ± 1.62	0.80 – 5.20

Correlations of hs-CRP with atheroclerosis severity

Plasma concentrations of hs-CRP in controls grop were higher than patients' group (Table 2). There's a significant hs-CRP level between controls and those who diagnose with atherosclerosis (p < 0.01). Level of hs-CRP in severe atherosclerosis was significantly higher than mild/moderate atherosclerosis, so there's was association between

hs-CRP concentration level and the severity of atherosclerosis.

Table 2: Level of hs-CRP in dyslipidemia patient and control

Group	n	hs-CRP μg/ml		p
		Mean ± SD	Median	
Controls	121	1.06 ± 1.63	0.48	
No Atherosclerosis	65	1.56 ± 1.55	0.75	0.132
Mild/Moderate Atherosclerosis	105	1.52 ± 1.77	0.56	0.005**
Severe Atherosclerosis	97	1.83 ± 1.60	1.31	0.001**

Related risk factor in hs-CRP serum levels

Univariate and multivariate analysis were used to examine and estimate the influence of clinical parameters which largely influencing the hs-CRP serum levels. As shown in Table 3, in a univariate analysis, fasting plasma glucose, triglyceride, an BMI were significantly positively correlated with hs-CRP levels. Whereas, HDL cholesterol was negatively correlated with hs-CRP levels. Then a multivariate regression analysis, using fasting plasma glucose, triglyceride, BMI, and HDL cholesterol as independent variables (model 1) all of which were significantly associated with hs-CRP in a univariate analysis, was carried out to determine the independent factors contributing to serum hs-CRP levels. As shown in Table 3, independent factors determining hs-CRP levels were triglyceride and BMI. Furthermore, a multivariate regression analysis including age and sex, as well as fasting plasma glucose, triglyceride, BMI, HDL cholesterol, as independent variables (Table 3, model 2), showed that independent factors for determining hs-CRP levels were sex, triglyceride, and BMI.

Table 3: Correlation of serum hs-CRP and a variety of clinical parameters and multivariate regression analysis to determine the independent factors contributing to hs-CRP levels in all subjects

hs-CRP	Univariate		Multivariate Model 1		Multivariate Model 2	
Related Risk Factor	ρ	p	t	p	t	p
Total cholesterol	0.056	ns				
LDL cholesterol	0.069	ns				
Triglyceride	0,257	< 0.0001	2.98	0.0029	3.03	0.0031
HDL cholesterol	-0.245	0.001	-1.16	ns	-1.31	ns
Fasting plasma glucose	0.160	0.009	1.21	ns	0.89	ns
BMI	0.254	< 0.0001	3.00	0.0302	2.40	0.0275
Hypertension	0.060	ns				
Diabetes	-0.158	ns				
Smoking	0.055	ns				
Age	0.145	ns			0.03	ns
Genders (male 1, female 2)					2.04	0.0321

Triglyceride, BMI, HDL cholesterol, fasting plasma glucose (model 1); triglyceride, BMI, HDL cholesterol, fasting plasma glucose, age and gender (model 2); BMI: Body Mass Index; LDL: Low Density Lipoproteins; HDL: High Density Lipoproteins.

Discussion

Our study clearly shows that there was an association between hs-CRP concentration and the severity of atherosclerosis. The value of hs-CRP in predicting atherosclerosis is noticeable in all ranges of atherosclerosis severity. Extensive atherosclerosis is relatively high risk regardless of hs-CRP levels. Some previous studies have shown a correlation between hs-CRP and the presence of atherosclerosis [13], whereas others have not found a correlation [14]. Although our result is consistent with hs-CRP being a marker of atherosclerosis, our data give no explanation about underlying process. Various hypotheses to explain the possible mechanism of which hs-CRP increasing the atherosclerotic risk have been proposed [15]. It has been thought that the development of atherosclerosis was led by serum hs-CRP level [5], [6], [7], [8], [9], [10], [11], [12]. C-reactive protein previously has been proposed to correlate with the extent of atherosclerosis [14]. Lower profile plaques were shown as numerous than “significant stenoses” in some studies and were statistically more likely to lead to plaque rupture than the relatively few lesions of > 70% stenosis [16]. Therefore, an elevated hs-CRP was possibly representing a more diffuse process of coronary atherosclerosis with a higher total plaque burden. If so, the predictive value of CRP would be considerably less after adjustment for extent of disease (total number of lesions) assessed by coronary angiography. So that the predictive value of hs-CRP must be adjusted for measures of all visible atherosclerotic plaques on angiography to exclude the possibility of an elevated CRP. On the other hand, if CRP levels primarily represent plaque properties (i.e., inflammation, instability), knowledge of CRP levels would continue to be useful even in the presence of angiographic assessment of plaque burden (extent / severity). Similarly, CRP and coronary calcium score (assessed by ultrafast computed tomography) may have independent and additive prognostic value, but this has not been extensively evaluated.

Hs-CRP proved to be the strongest and most significant predictor of the risk of future cardiovascular events [17]. Even though several new pharmacological approaches have been introduced to reduce the hs-CRP levels [15]. [18], [11], [3], there are still many cardiovascular diseases all over the world. Hs-CRP and the ratio of total cholesterol to HDL cholesterol were found to be independent predictors of risk in models in which women were matched for smoking status and age or in models that included further adjustments for body-mass index, hypertension, diabetes, and parental history of premature coronary artery disease [11]. In our present study, we found that independent factors for determining hs-CRP levels are triglyceride, BMI, and fasting plasma glucose. Thus, it is important to undergo a strict management of atherosclerosis related risk factors, which were triglyceride, fasting plasma glucose and BMI, to reduce serum hs-CRP levels in patients with dyslipidemia. Multivariate regression analysis showed that triglyceride and BMI were independent risk factors determining hs-CRP levels (Table 3). These results suggest that high triglyceride and high BMI are closely associated with

high serum hs-CRP levels in patients with dyslipidemia.

Quantification of atherosclerosis findings was limited to the visual interpretation of the attending cardiologist, which is representative of “real world” practice. Intravascular ultrasound could be expected to give increased measures of atherosclerotic burden by identifying “intramural plaques,” although this would be impractical to apply routinely.

The significant differences between hs-CRP concentrations in our study, depending on the severity of atherosclerosis, give some evidence for a possible function of hs-CRP protein as an epidemiological risk marker. They support the hypothesis of a causal relationship between an acute phase reaction and the pathogenesis of atherosclerosis in coronary arteries and other parts of the arterial vessel system. High triglyceride and BMI is closely associated with high hs-CRP level in patients with dyslipidemia. We should consider this point in practical medicine, and thus the data in the present study results would provide important information from a clinical point of view.

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