

The levels of hs-CRP in patients with coronary heart disease

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Abstrak

Aterosklerosis sebagai penyebab terjadinya PJK merupakan proses multifaktorial karena banyak sekali faktor-faktor yang menyebabkannya dengan mekanisme yang saling terkait. Saat ini proses aterosklerosis dianggap sebagai proses inflamasi. Inflamasi terbukti berperan penting pada inisiasi, progresi maupun destabilisasi plak aterosklerosis. High sensitivity C-reactive protein (hs-CRP) merupakan salah satu petanda inflamasi yang penting pada penyakit jantung koroner (PJK) yang berhubungan dengan tingkat keparahan aterosklerosis, iskemi miokardium dan nekrosis miokardium. Tujuan penelitian ini adalah untuk mengetahui dan membandingkan kadar hs-CRP pada pasien sindroma koroner akut (SKA), PJK kronik dan bukan PJK, serta untuk mengetahui apakah terdapat hubungan antara kadar hs-CRP dengan kadar enzim CKMB pada pasien infark miokard akut (IMA). Penelitian bersifat observasional deskriptif dan analitik dengan pendekatan potong lintang. Dilakukan pemeriksaan kadar hs-CRP dengan metode chemiluminescent pada 21 pasien SKA, 20 pasien PJK kronik dan 20 bukan PJK. Didapatkan kadar hs-CRP rerata pada pasien SKA, PJK kronik dan bukan PJK sebesar 8,40 (SD 5,53) mg/l, 2,81 (SD 2,09) mg/l dan 1,07 (SD 0,81) mg/l. Analisis statistik didapatkan perbedaan kadar hs-CRP yang bermakna antara pasien SKA, PJK kronik dan bukan PJK ($p < 0,000$). Kadar hs-CRP mempunyai korelasi positif yang bermakna dengan kadar enzim CKMB pada pasien IMA ($p < 0,004$). Sebagai kesimpulan, kadar hs-CRP pada pasien SKA secara bermakna lebih tinggi dibanding PJK kronik dan bukan PJK. Terdapat hubungan yang bermakna antara peningkatan kadar hs-CRP dengan peningkatan kadar enzim CKMB. (*Med J Indones 2004; 13: 102-6*)

Abstract

Coronary heart disease (CHD) due to atherosclerosis is a multifactorial process with multiple interdependent factors. At present time, atherosclerosis is considered to be an inflammatory process. It has been proven that inflammation plays a mayor role in the initiation, progression as well as the destabilitation of the atherosclerosis plaque. High sensitivity C-reactive protein (hs-CRP) is one of the most important inflammatory marker in CHD and directly related to the extent and severity of atherosclerosis, extent of myocardial ischemia and myocardial necrosis. The purpose of this study is to determine hs-CRP levels in patients with acute coronary syndrome (ACS), chronic CHD and non CHD. And, to determine the correlation between hs-CRP levels and CKMB enzyme level in patients with acute myocardial infarction (AMI). This is a descriptive observational analytic study with cross sectional design. hs-CRP levels were measured by using chemiluminescent method on 21 ACS patients, 20 chronic CHD patients and 20 non CHD patients. The mean hs-CRP level in ACS, chronic CHD and non CHD patients were respectively 8.40 (SD 5.53) mg/l, 2.81 (SD 2.09) mg/l and 1.07 (SD 0.81) mg/l. A statistically significant difference in hs-CRP level was found between ACS, chronic CHD and non CHD ($p = 0.000$). A positive correlation was found between hs-CRP level and CKMB enzyme level in AMI patients ($p = 0.004$). In conclusion hs-CRP level is consistently higher in patients with ACS compared to patients with chronic CHD and non CHD. A positive correlation was found between the increased level of hs-CRP and CKMB enzyme level. (*Med J Indones 2004; 13: 102-6*)

Keywords: atherosclerosis, inflammation, hs-CRP, CHD

According to the current concept, atherosclerosis process is more considered as inflammation process rather than only the consequence of fat accumulation at the vessel walls.^{1,2} The finding of T lymphocytes, monocytes, macrophages and mast cells in atherosclerotic

lesions and secretion of cytokines obviously showed the evidence of inflammation element in atherosclerotic process.²⁻⁵ Unstable atherosclerotic plaque that later became rupture and caused ACS was also due to the existence of inflammation response in the form of activated T lymphocytes, increase CRP and other inflammation markers.^{2,5,6} Van der Wall et al⁷ reported that there was inflammation cells quantity increase (macrophages, T lymphocytes, and mast cells) at rupture plaque. Liuzzo et al⁸ reported that hs-CRP

level and serum amyloid A protein (SAA) in unstable angina pectoris (UAP) patients was higher than in stable angina pectoris patients and the height of hs-CRP level served as poor indicator of patient prognosis. de Beer et al⁹ said that there was a significant correlation between hs-CRP level and CKMB enzyme level in AMI patients.

Age, sex, blood lipid levels, hypertension and diabetes influence on hs-CRP level was not clear. According to Yeh and Willerson,¹⁰ age and sex did not affect hs-CRP levels. Haverkate et al¹¹ said that age and triglycerides level affect hs-CRP level, but blood cholesterol level, hypertension and diabetes did not affect hs-CRP level, whereas according Rifai¹² and Pierson et al,¹³ hypertension and diabetes did affect hs-CRP levels. According to Ridker,¹⁴ blood lipid levels did not affect hs-CRP levels. Obesity (measured by BMI) can increase hs-CRP level, but its mechanism was not clear yet. One of the possibilities was because adipose tissue can produce proinflammatory cytokines. Smoking can increase hs-CRP levels, IL-6 and ICAM-1, while stop smoking can decrease the inflammation markers levels.^{12,15}

Statin and aspirin as antiinflammation were obviously effective in both primary and secondary CHD prevention.^{16,17}

METHODS

This study was carried out from May to September 2003 in Cardiology Division Manado General Hospital. The study population comprised of ACS, chronic CHD

and non CHD patients. Inclusion criteria were ACS patients (UAP and AMI with onset 4-24 hours from start of chest pain and did not obtain thrombolysis therapy yet), chronic CHD and non CHD. Exclusion criteria were patients suffering from infection disease, arthritis, renal failure, malignancy, liver disease, rheumatic fever, blood diseases such as leukaemia, patients who received transplantation and pregnant, patients who receiving statin drugs, NSAIDs, antibiotics, corticosteroids, immunosuppressive therapy and estrogen. hs-CRP level examination was carried out by using chemiluminescent (Immulite) method with normal value < 1,1 mg/l. Data analysis used was variance analysis (Anova) to find out the hs-CRP levels difference in ACS, chronic CHD and non CHD patients. If the result was significant the analysis was continued with least significant difference (LSD) test. The t independent test was used to find out the hs-CRP levels difference in UAP and AMI patients. The regression analysis was used to find out the relationship between hs-CRP level and CKMB enzyme level in AMI patients.

RESULTS

During the study 61 patients were found, consisting of 21 ACS patients, 20 chronic CHD patients and 20 non CHD patients. The characteristics data of the three patient groups can be seen in Tables 1 and 2. No significant difference of age, sex, BMI, hypertension, smoking, total cholesterol level, LDL, HDL and triglycerides between ACS, chronic CHD, non CHD patients and between UAP and AMI patients.

Table 1. Characteristics data of ACS, chronic CHD and non CHD patients

	ACS [n = 21]	Chronic CHD [n = 20]	Non CHD [n = 20]	p value
Age [yrs]	61,48 (10,26)	61,95 (6,15)	60,25 (6,74)	0,785
Sex [♂ / ♀]	15 / 6	14 / 6	14 / 6	0,993
BMI [kg/m ²]	26,59 (3,32)	26,32 (4,24)	25,86 (2,66)	0,796
Hypertension[%]	76,2	85	75	0,699
Smoking [%]				0,960
- Active*	33,3	30	40	
- Past “	38,1	40	30	
- Never	28,6	30	30	
Total Cholest	214,24 (30,94)	219,55 (49,49)	200,30 (35,94)	0,288
LDL	144,00 (29,65)	149,51 (54,81)	127,66 (37,57)	0,236
HDL	41,24 (7,28)	41,35 (8,97)	45,50 (8,31)	0,179
Triglycerides	145,00 (41,93)	143,45 (46,35)	135,70 (38,48)	0,757

() : standard deviation

* Active : still smoking up to 1 month ago,¹¹

“ Past : stopped smoking longer than 1 month ago¹¹

Table 2. Characteristics data of ACS patients (UAP and AMI)

	UAP [n = 10]	AMI [n = 11]	p value
Age [yrs]	60,90 (8,47)	62,00 (12,05)	0,813
Sex [♂ / ♀]	7 / 3	8 / 3	0,633
BMI [kg/m ²]	27,01 (4,19)	26,20 (2,43)	0,590
Hypertension [%]	80	72,7	0,550
Smoking (%)			0,953
- Active*	30	36,4	
- Past “	40	36,4	
- Never	30	27,2	
Total Cholest	218,30 (32,67)	210,55 (30,38)	0,580
LDL	148,88 (32,45)	139,56 (27,65)	0,486
HDL	40,00 (7,76)	42,36 (6,99)	0,472
Triglycerides	147, 10 (44,44)	143,09 (41,61)	0,833

The mean hs-CRP level in ACS, chronic CHD and non CHD patients were respectively 8.40 (SD 5.53) mg/l, 2.81 (SD 2.09) mg/l and 1.07 (SD 0.81) mg/l. A statistically difference in hs-CRP level was found between ACS, chronic CHD and non CHD ($p = 0.000$). When ACS was compared to chronic CHD, a statistically significant difference in hs-CRP level was found ($p = 0.000$). No statistically significant difference in hs-CRP level was found when comparing chronic CHD and non CHD ($p = 0.363$) (Figure 1). Mean hs-CRP level in UAP and AMI patients were respectively 4.90 (SD 2.21) mg/l and 11.57 (SD 5.78) mg/l. Statistic analysis result with t independent test showed significant hs-CRP levels difference between UAP and AMI patients ($p = 0.003$) (Figure 2).

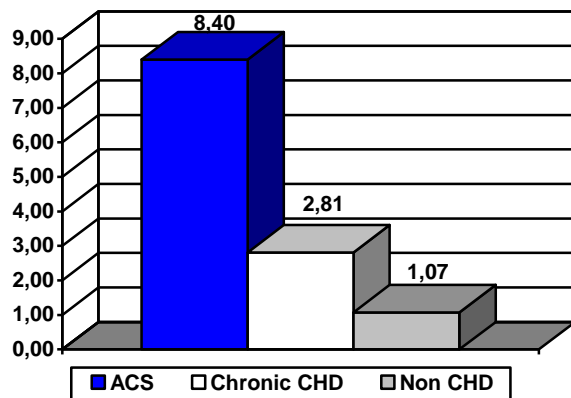


Figure 1. Comparison of mean hs-CRP levels in patients with ACS, Chronic CHD and Non CHD

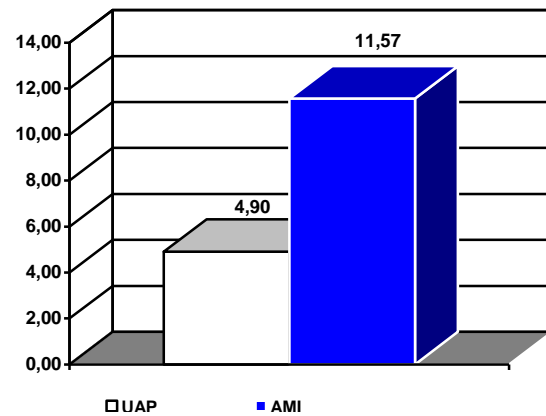


Figure 2. Comparison of mean hs-CRP levels in patients with Unstable AP and AMI

Statistical analysis result with regression analysis to find out the relationship between hs-CRP level and CKMB enzyme level in AMI patients indicated positive correlation with correlation coefficient value $r = 0.783$. This result showed that the higher the CRP level, the higher the CKMB enzyme level (Figure 3).

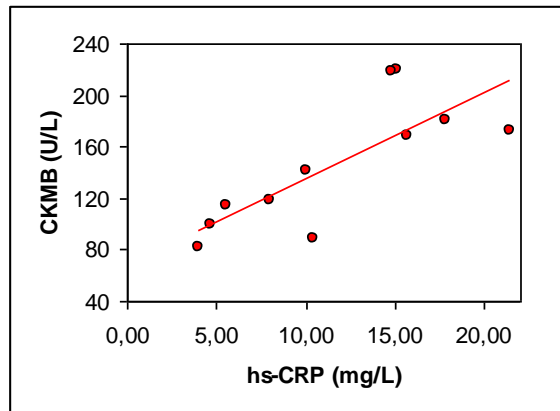


Figure 3. Correlation between hs-CRP level and CKMB enzyme level

DISCUSSION

Inflammation process in atherosclerosis can increase acute phase protein levels produced by the liver with cytokines stimulation (particularly IL-6, IL-1 and TNF- α). The cytokines produced by activated macrophages, activated vessel wall cells (especially endothelial cells and smooth muscle cells) and other cells.^{11,18,19} During inflammation the two most sensitive acute phase protein levels were CRP and SAA could increased, but SAA showed less significant correlation with CHD and variation result were higher than CRP. Acute phase proteins could also increase in infection and tissue damage.^{11,20}

Age, sex, blood lipid levels and diabetes influence on hs-CRP level was not clear but obesity and smoking could increase hs-CRP levels.^{12,15} hs-CRP level in former smoker was the same as hs-CRP level in people who had never smoked.²¹ In this study, no significant difference was found in term of age, sex, BMI, hypertension, smoking, total cholesterol level, LDL and triglycerides between ACS, chronic CHD and non CHD patients but the total cholesterol level, LDL and triglycerides mean in non CHD was lower while HDL was higher.

Inflammation proved to have an important role in initiation, progression as well as atherosclerotic plaque destabilization.^{5,12,16} Activated T lymphocyte cells percentage was higher in atherosclerotic lesion of UAP and AMI patients than in stable angina pectoris patients. This condition indicated that there were recent activity and immune response increase in plaque.⁷ hs-CRP showed inflammation and is directly

related to the extent and severity of atherosclerosis, extent of myocardial ischemia (angina) and myocardial necrosis (AMI). hs-CRP level in UAP patients was higher than in stable angina pectoris patients and hs-CRP levels in those two groups was higher than in non CHD groups.^{8,20}

The mean hs-CRP level in chronic CHD patients in this study was 2.81 (SD 2.09) mg/l. This result was lower than the result reported by Ridker et al²² who found the mean hs-CRP level in chronic CHD patients 3.6 mg/l but higher than the one reported by Haverkate et al¹¹ who found mean hs-CRP level 1.68 mg/l. According to Pasceri et al²³ the risk of AMI in stable angina pectoris patients with hs-CRP level > 3.6 mg/l was twice as high as in patients with hs-CRP level < 3.6 mg/l.

The mean hs-CRP level in non CHD in this study was 1.07 (SD 0.81) mg/l. This result was not significantly difference from that reported by Berk et al²⁴ who found the mean hs-CRP level in non CHD 0.9 mg/l. In healthy people hs-CRP level correlated with the risk of future cardiovascular events. hs-CRP levels of <1, 1 to 3, and >3 mg/l correspond to low, moderate and high risk groups for future cardiovascular events. hs-CRP levels >10 mg/l in healthy people indicated occult infection or other systemic inflammatory process so that hs-CRP examination should be carried out again one month later or after the infection was recovered.^{10,14}

Kennon et al²⁵ found the mean hs-CRP level in UAP patients 4.57 mg/l, whereas Mach et al¹⁸ found it in UAP and AMI 5.0 mg/l and 17.0 mg/l. According to Maseri et al²⁶ hs-CRP level in UAP patients could be used to predict the course of the disease. hs-CRP level >3 mg/l and in particular if > 10 mg/l can predict poor response toward intensive care and indicated high risk to AMI events.

In this study it was found that the mean hs-CRP level in UAP and AMI patients was 4.09 (SD 2.21) mg/l and 11.57 (SD 5.78) mg/l and statistic analysis result showed significant difference ($p = 0.000$). The mean hs-CRP level in UAP patients in this study did not differ much from the above result, while the mean hs-CRP level in AMI patients in this study was lower than that reported by Mach et al.¹⁸ This was probably due to interindividual variation. According to de Maat et al²⁷ response from hs-CRP showed interindividual variation in which there were high responders and low responders patients.

High hs-CRP level in AMI patients showed more intensive inflammation reaction that dealt with myocardial tissue damage extent (myocardial necrosis).^{20,27,28} de Beer et al⁹ reported that there was significant correlation between hs-CRP level and CKMB enzyme level in AMI patients. This was an accordance with the result of this study in which there was significant positive correlation between hs-CRP level and CKMB enzyme level in AMI patients.

CONCLUSION

hs-CRP level is consistently higher in patients with ACS compared to patients with chronic CHD and non CHD. hs-CRP level is consistently higher in patients with chronic CHD in comparison to non CHD but no statistically significant difference was found. hs-CRP level is consistently higher in patients with AMI in comparison to UAP patients. A positive correlation was found between the increase level of hs-CRP and CKMB enzyme level.

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