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Relationship between Cardiac Rehabilitation and High Sensitivity C-Reactive Protein in Patients undergoing Coronary Artery Bypass Graft Surgery

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Abstract : Background : Coronary heart disease (CHD), a gradual chronic inflammatory disease, is influenced by the environmental, lifestyle, and genetic factors that can be seen from traditional risk factors, inflammatory biomarkers, and metabolic status.Inflammatory biomarkers that were currently being studied include high sensitivity C-reactive protein (hsCRP), interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-α), and intercellular adhesion molecule-1 (ICAM-1). Increased hsCRP is an independent risk factor that is important for CHD and determines the prognosis in patients who have CHD. Cardiac rehabilitation has a role in improving risk factors and preventing a variety of advanced cardiovascular events. This study aims to find the relationship of cardiac rehabilitation programs to hsCRP values in patients with CHD who have undergone coronary artery bypass grafting (CABG).**Methods** :This study was conducted from April 2018 - September 2018 with a total sample of 67 patients underwent phase II cardiac rehabilitation programs following CABG that met the inclusion and exclusion criteria. The hsCRP laboratory examination was conducted by the Clinical Pathology Laboratory of Haji Adam Malik General Hospital in two measurement periods, before and after the phase II cardiac rehabilitation program. And then the data was analyzed to see the relationship between cardiac rehabilitation and hsCRP value.**Results**: The total subjects of this study were 67 people that can be classified into two groups, high risk group (hsCRP >3 mg/dL)15 people (22.38%) and medium risk group (hsCRP 1-3 mg/dL)52 people (77.61%). Statistically significant improvements were found with p <0.05 in various parameters such as: body weight, body mass index (BMI), waist circumference, six minutes walk distance (6MWD), functional capacity, hsCRP value, total cholesterol, LDL, HDL, and TG. Negative correlation was obtained between hsCRP value and functional capacity before the program with r -0.689 and p <0.05. A negative correlation was found between hsCRP value and functional capacity after the program with r -0.819 and p <0.05.**Conclusion** : There was a relationship between cardiac rehabilitation and hsCRP in patients undergoingCABG. A significant decrease of hsCRP value was found in this study. Cardiac rehabilitation program not only improved laboratory components such as hsCRP and lipid profile, but also improved other metabolic parameters such as weight, BMI, waist circumference, and also improved the 6MWD and exercise capacity of patients after CABG. There was a statistically significant negative correlation between hsCRP values and functional capacity both before and after the rehabilitation program.
Keywords : cardiac rehabilitation, hsCRP, CABG, CHD.

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Introduction:

C-Reactive Protein (CRP)was a very stable protein and has been measured in various laboratories over the past few decades to assess the process of active or inflammatory infections. Recently developed method ishigh-sensitivity C-reactive protein (hsCRP) because it can measure CRP values at a very low concentration. HsCRP can predict the incidence of myocardial infarction, stroke, peripheral artery disease, and sudden cardiac death among normal people without a history of heart disease[1].

Pathological examination has showed that inflammation played a role in the atherosclerosis process. Epidemiological data suggested persistent mild inflammation was an independent predictor of coronary heart disease (CHD). Scientist claimed CRP not only as an indirectbut also direct marker of vascular inflammation in the etiology of atherosclerosis. Increased CRP was an important independent risk factor for coronary heart disease and determines the prognosis in patients who have coronary heart disease[2].

Cardiac rehabilitation is a coordinated intervention on various aspects designed to optimizecardiovascular patients in physical, psychological, and social functions, in addition to stabilizing, slowing, or even reversing the progression of the atherosclerotic process, so that it will reduce morbidity and mortality. In 1994, the American Heart Association (AHA) declared that cardiac rehabilitation should not only be limited to exercise program butalsoinclude a variety of strategies aimed at improving the risk factors for modifiable cardiovascular disease[3].

Some evidence have showed the anti-inflammatory effects of exercise on biomarkers such as hsCRP in various conditions and populations. Cardiac rehabilitation that includes exercise prescription, health education, and psychological counseling has shown good physical and psychosocial results for patients with CHD[4]. Weight loss and exercise were effective in reducing vascular inflammation, which can be seen from the declined CRP. Biological mechanisms involved include improvements in body weight, lipid profile, blood pressure, glycemic control, and fibrinolytic activity. Participation in a cardiac rehabilitation program showed a 31% reduction in cardiovascular deaths and 27% of total deaths[2].

Studies have shown that inflammatory marker such as hsCRPwas an alternative method for cardiovascular risk assessment in general. Several prospective studies have shown plasma hsCRP values as a strong predictor of risk of cardiovascular events in individuals with or without cardiovascular disease, including patients who have returned home after acute coronary syndrome[5].

Methods

Study Design and Population

This study was a prospective cohort study in Haji Adam Malik General Hospital with permission from the Research Ethics Committee of the Faculty of Medicine University of North Sumatra and Haji Adam Malik General Hospital. The study was conducted from April 2018 to September 2018on patients undergoing phase II cardiac rehabilitation program following coronary artery bypass grafting (CABG) at Haji Adam Malik General Hospital.

The inclusion criteria for this study is ambulatory CABG patients who followed ≥90% of phase II cardiac rehabilitation program. hsCRP laboratory examination was carried out by the Clinical Pathology Laboratory of Haji Adam Malik Hospital. The tools that were used are Abbott Architect and measurements are made by turbidimetric/immunoturbidimetric methods.Patients with severe inflammatory infections or processes, patients with worsening symptoms of congestive heart failure, patients with liver dysfunction, patients with kidney failure, patients with malignancy, patients with cognitive impairment and patients with hsCRP values before the program <1 mg/dL were excluded from this study.

After CABG, all subjects must beinvolved in phase I cardiac rehabilitation. When they are planned for discharge, they will be reeducated to undergo a phase II cardiac rehabilitation. Then the purpose of the study was explained and the subjects were asked to sign an informed consent. After that, measurements of various parameters are needed including sCRP, body mass index (BMI), and 6MWD. Then the patientswill be given exerciseprescription to be carried out independently at home.

The phase II cardiac rehabilitation at Haji Adam Malik General Hospitalwas conducted in the gym 3 times per week for 4 weeks. The type of exercise was aerobic such as walking lightly,walking slowly on treadmill, and cycling on ergocycle. Each session was preceded by a warming-up session and ended with cooling-down session. The duration of each session was at least 30 minutes and the type of exercise is adjusted to the patient's ability. In addition to exercise process, patients also underwent counseling once per week for discussing the progress and difficulties felt by patients, recommendations on diet and lifestyle, and motivation to increase adherence to the program. During the cardiac rehabilitation, all patient examination and therapy data were fully recorded.

After completing the phase II cardiac rehabilitation program, patients were advised to undergo a treadmill test for evaluation. The measurement of various parameters were needed such as hsCRP, BMI and 6MWD. And then the subjects were educated about permissible activities, recommended exercise, and exerciseprescription to be practiced. The data from the study was analyzed with SPSS.

Data Analysis

The Kolmogorov-Smirnov and Saphiro-Wilk tests were used to determine the normality of data distribution. Data presentations for categorical variables were made in the form of percentage (%) while for numeric variables with normal distribution will be made in the form of mean ± standard deviation (SD), and in the form of mean ± standard error (SE) if the data was not normally distributed. Categorical variables were compared using the Chi-Square test (normally distributed data) or the Fischer Exact test (not normally distributed).The numerical hsCRP groups, namely the group before and after the rehabilitation program were assessed by paired T test which is used to compare the data with normal distribution and Wilcoxon test if not normally distributed. Pearson correlation test (normally distributed data) and Spearman (not normally distributed data) were used to assess the correlation between rehabilitation program and hsCRP. Significantly different statistics were defined as $p<0.05$.

Results

The subjects of this study were 67 patients undergoing phase II cardiac rehabilitation programfollowing CABG that met the inclusion and exclusion criteria. Baseline characteristics of the subjects were summarized in Table 1 .

Table1. Baseline Characteristics of the Subjects Undergoing Cardiac Rehabilitation ProgramFollowing CABG

Variable	Value
Women (n, %) Men (n, %)	9 (13,4) 58 (86,6)
Age (years ± SD)	56,83 ± 8,18
Body Mass Index (kg/m² ± SD)	26,31 ± 3,88
Waist Circumference (cm ± SD)	88,10 ± 8,9
Metabolic Syndrome (n, %)	23 (34,3)
Tobacco Use (n, %)	46 (68,7)
DiabetesMelitus (n, %)	22 (32,8)
Hypertension (n, %)	42 (62,7)
Dyslipidemia (n, %)	45 (67,2)
Menopause (n, %)	8 (11,9)
Sedentary Lifestyle (n, %)	26 (38,8)
Overweight (n, %)	38 (56,7)
Family History (n, %)	10 (14,9)
Statin Use (n, %)	52 (77,6)
Cardiomegaly (n, %)	42 (62,7)
Six Minutes Walk Distance (meter ± SD)	462,16 ± 166,17
Exercise Capacity (METs ± SD)	3,2 ± 0,79

hsCRP (mg/dL ± SD)	2,69 ± 1,53
Ejection Fraction (% ± SD)	50,58 ± 6,9
Total Cholesterol (mg/dL ± SD)	174,03 ± 38,39
High-density Lipoprotein (HDL) (mg/dL ± SD)	38,82 ± 9,19
Low-density Lipoprotein (LDL) (mg/dL ± SD)	116,15 ± 39,5
Triglyceride (TG) (mg/dL ± SD)	162,21 ± 59,48

The baseline characteristics then divided into two criteria based on cardiovascular risk stratification (Table 2). In the high risk group (hsCRP >3 mg/dL) there were 2 women (13.3%) and 13 men (86.7%), while in the moderate risk group (hsCRP 1-3 mg/dL) there were 7 women (13.5%)and 45 men (86.5%). According to risk factors, the only statistically significant risk was dyslipidemia with p value 0.014 [14 people in high risk group (93.3%) vs.31 people in moderate risk group (59.6%)].

According to 6MWD, there was significant difference between the two groups with $p < 0.05$[179±105.15 meters in the high risk group vs. 543.84±48.1 meters in the moderate risk group]. According to exercise capacity, there was significant difference between the two groups with $p < 0.05$ [1.85±0.5 METs in high risk group vs.3.59±0.22 METs in moderate risk group]. Based onhsCRP value, there was significant difference between the two groups with $p < 0.05$ [1.85±0.5 mg/dL in high risk group vs. 2.11±0.54 mg/dL in moderate risk group].

Based on ejection fraction, there was significant difference between the two groups with p value 0.012 [46.67±7.54% in high risk group vs. 51.71±6.37% in moderate risk group]. Based on total cholesterol, there was significant difference between the two groups with p value 0.014 [186.86±34.5 mg/dL in high risk group vs. 170.32±38.94 mg/dL in moderate risk group]. Based on LDL, there was significant difference between the two groups with p value 0.038 [134.66±34.72 mg/dL in high risk group vs. 110.8±39.4 mg/dL in moderate risk group].

Table2.Baseline Characteristics Based on Cardiovascular Risk Stratification

Variable	***High Risk*** **(hsCRP >3 mg/dL) (n=15)**	***Moderate Risk*** **(hsCRP 1-3 mg/dL) (n=52)**	**p value**
Women (n, %) Men (n, %)	2 (13,3) 13 (86,7)	7 (13,5) 45 (86,5)	1,00
Age (years ± SD)	58,26 ± 5,13	56,42 ± 8,7	0,314
Body Mass Index (kg/m² ± SD)	26,86 ± 3,62	26,15 ± 3,97	0,534
Waist Circumference (cm ± SD)	88,7 ± 8,7	87,9 ± 9	0,759
Metabolic Syndrome (n, %)	6 (40)	17 (32,7)	0,759
Tobacco Use (n, %)	11 (73,3)	35 (67,3)	0,76
Diabetes Melitus (n, %)	5 (33)	17 (32,7)	1,00
Hypertension (n, %)	8 (53,3)	34 (65,4)	0,395
Dyslipidemia (n, %)	14 (93,3)	31 (59,6)	0,014*
Menopause (n, %)	2 (13,3)	6 (11,5)	1,00
Sedentary Lifestyle (n, %)	5 (33,3)	21 (40,4)	0,76
Overweight (n, %)	9 (60)	29 (55,8)	0,77
Family History (n, %)	2 (13,3)	8 (15,4)	1,00
Statin Use (n, %)	14 (93,3)	38 (73,1)	0,164
Cardiomegaly (n, %)	11 (73,3)	31 (59,6)	0,33
6MWD (meter ± SD)	179 ± 105,15	543,84 ± 48,1	0,000*
Exercise Capacity (METs ± SD)	1,85 ± 0,5	3,59 ± 0,22	0,000*
hsCRP (mg/dL)	4,7 ± 2,12	2,11 ± 0,54	0,000*
EjectionFraction (% ± SD)	46,67 ± 7,54	51,71 ± 6,37	0,012*
Total Cholesterol (mg/dL ± SD)	186,86 ± 34,5	170,32 ± 38,94	0,014*
HDL (mg/dL ± SD)	36,3 ± 9,25	39,5 ± 9,13	0,237
LDL (mg/dL ± SD)	134,66 ± 34,72	110.8± 39.4	0,038*
TG (mg/dL ± SD)	146,2 ± 54,66	161,63 ± 61,3	0,884

After the subjects completed the program, those variables were measured again. Then a statistical analysis was performed to assess the changes that occur. In Table 3, the differences in variables can be observed. There were a statistically significant changes in body weight [(p value <0.05) 68.78±11.08 kg vs. 67.65±10.72 kg]; BMI [(p value <0.05) 26.31±3.88 kg/m² vs. 25.87±3.67 kg/m²]; waist circumference [(p <0.05) 88.10±8.92 cm vs. 87.44±8.58 cm]; 6MWD [462.16±166.17 m vs. 745.52±134.79 m(p <0.05)]; exercise capacity [3.20±0.79 METs vs. 4.55±0.64 METs(p <0.05)] and hsCRP[2.69±1.53 mg/dLvs. 0.90±1.05 mg/dL(p <0.05)].

Apparently all the lipid profile components experienced a statistically significant change with p<0.05. First, total cholesterol value[174.02±38.39 mg/dLvs. 160.46±37.61 mg/dL]; second, LDL value [116.14±39.50 mg/dLvs. 100.46±30.97 mg/dL]; third, HDL value 38.82±9.19 mg/dLvs. 48.85±12.22 mg/dL]; andfourth, TG value [162.20±59.48 mg/dLvs. 147.16±62.05 mg/dL].

Table3.Variables Comparation Before and After Cardiac Rehabilitation (CR)

Variable	Before CR	After CR	p value
Weight (kg ± SD)	68,78 ± 11,08	67,65 ± 10,72	0,000*
BMI (kg/m² ± SD)	26,31 ± 3,88	25,87 ± 3,67	0,000*
Waist Circumference (cm ± SD)	88,10 ± 8,92	87,44 ± 8,58	0,000*
6MWD (meter ± SD)	462,16 ± 166,17	745,52 ± 134,79	0,000*
Exercise Capacity (METs ± SD)	3,20 ± 0,79	4,55 ± 0,64	0,000*
hsCRP (mg/dL ± SD)	2,69 ± 1,53	0.90 ± 1,05	0,000*
Total Cholesterol (mg/dl ± SD)	174,02 ± 38,39	160,46 ± 37,61	0,000*
LDL (mg/dl ± SD)	116,14 ± 39,50	100,46 ± 30,97	0,000*
HDL (mg/dl ± SD)	38,82 ± 9,19	48,85 ± 12,22	0,000*
TG (mg/dl ± SD)	162,20 ± 59,48	147,16 ± 62,05	0,000*

Figure 1 summarize the changes in hsCRP values before and after phase II cardiac rehabilitation program which is divided based on certain characteristics. In the men-women groups we can observe the initial value of hsCRP before the program was not much different, the women's group was only slightly higher than the male group. However, after the program, we found a significant decrease in hsCRP values in both groups which was indicated by p value 0.01 in the female group and p <0.05 in the male group. In the elderly-nonelderly groups, we can observe that the initial value of hsCRP before the program was higher in the elderly group. However, after the program, we found a significant decrease in hsCRP values in both groups marked by a p <0.05.

In the metabolic syndrome-non metabolic syndrome groups,hsCRP value before the program was higher in metabolic syndrome. However, after the program, there was a significant decrease in hsCRP values in the two groups marked with a p <0.05. In the weight gain-weight loss groups, hsCRP value before the program was higher in weight loss. However, after the program, there was a significant decrease in hsCRPin the weight gain(p value 0.013)and in the weight loss (p <0.05) group.

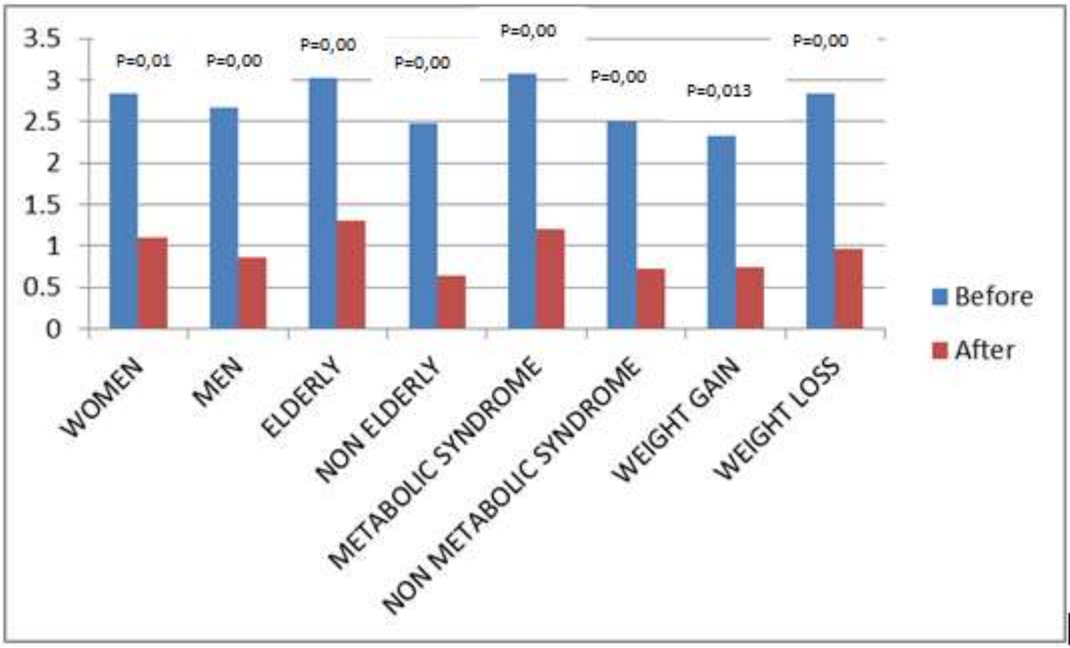

Figure 1 . hsCRP Values Before and After Cardiac Rehabilitation Based On Certain Characteristics

CorrelationofhsCRP and exercise capacity measured before program can be seen in Table 4. Negative correlation was obtained with r -0.689 and p<0.05. The r value shows astrong correlation statistically.

Table 4. Correlation of hsCRP and Exercise Capacity Before Cardiac Rehabilitation

hsCRP	r pearson	p value
Exercise Capacity (METs)	- 0,689	0,000*

CorrelationofhsCRP and exercise capacity measured after program can be seen in Table 5. Negative correlation was obtained with r -0.819 and p<0.05. The r value shows avery strong correlation statistically.

Table5.Correlation of hsCRP and Exercise Capacity After Cardiac Rehabilitation

hsCRP	r pearson	p value
Exercise Capacity (METs)	- 0,819	0,000*

Discussion

The majority of subjects undergoing phase II cardiac rehabilitation following CABG are male, smoker, have history of hypertension, dyslipidemia, overweight, cardiomegaly, have low exercise capacity, have moderate cardiovascular risk, low HDL, and high TG.

We can found more dyslipidemic patients, lower 6MWT distance, lower exercise capacity, higher hsCRP, lower ejection fraction,higher total cholesterol, and higher LDL in the high risk group. This is consistent with a study conducted by Saito et al. which stated that the hsCRP value was influenced by various traditional risk factors for cardiovascular disease, including age, smoking, obesity, hypertension, and dyslipidemia which would accelerate the process of atherosclerosis and trigger cardiovascular diseases such as CHD[6]. Nyandak et al. also mentioned that higher hsCRP values were associated with disease burden in CHD patients[7].

There was a statistically significantchange(p<0.05) towardbetter values at some variables such as body weight, BMI, waist circumference, 6MWD, exercise capacity, hsCRP, total cholesterol, LDL, HDL and TG. A study conducted by Cesari et al. with subjects who underwent a short period of cardiac rehabilitation (only 15 days) following CABG proved that the program could significantly reduce levels of cytochemokines, CRP and NT-proBNP[8]. Caulin-Glaser et al. also conducted a study of 172 CHD patients undergoing cardiac rehabilitation programs. The patients then showed significant improvement in BMI, exercise capacity, HDL, and CRP[2]. Milani et al. conducted a study of 277 CHD patients undergoing a formal phase II cardiac rehabilitation program for three months. There was a significant improvement in body fat, exercise capacity, and hsCRP[5].

The hsCRP value before and after phase II cardiac rehabilitation program had a statistically significant improvement ($p<0.05$) in various group characteristics such as men-women, elderly-nonelderly, metabolic syndrome-non metabolic syndrome, and weight gain-weight loss. McBride et al. have conducted research involving patients with metabolic syndrome and diabetes mellitus. Lifestyle changes and regular exercise were advisedand then observed for one year. Significant changes in body weight, BMI, body fat percentage and waist circumference were found[9]. Beckie et al. had conducted a study on 91 women with CHD in a cardiac rehabilitation program for 12 weeks. There was significant decrease in inflammatory biomarker such ashsCRP, IL-6, TNF-α, and ICAM-1[4]. Lavie et al. conducted a study of 235 CHD patients with obesity. Patients were included in a formal cardiac rehabilitation program. Improved body weight, BMI, fat percentage, exercise capacity, HDL, CRP and quality of life were found[10]. Onishi et al. conducted a study of 32 patients with metabolic syndrome who had undergone CABG. These patients were included in cardiac rehabilitation program for six months. There was a significant decrease in waist circumference, body weight, fat weight, percentage of fat, total cholesterol, LDL, and hsCRP. There were also improvements in exercise capacity, muscle strength, and inflammatory status[11].

Negative correlation was obtained between hsCRP value and exercise capacity before the program with r value of -0.689 and $p<0.05$ which indicates that if the hsCRP value decreases then the functional capacity will increase and vice versa. A negative correlation was found between hsCRP value and functional capacity after the program with r value of -0.819 and $p<0.05$ which also showed that if the hsCRP value decreases then the functional capacity will increase and vice versa. The results of this study are in accordance with the study by Rahimi et al. The study was conducted in stable CHD patients who had been diagnosed with coronary angiography and functional capacity assessed by maximal exercise testing. The results of this study indicate that exercise capacity has a negative correlation with hsCRP values regardless of the severity of CHD and the use of standard drugs[12].

Study Limitations

The number of subjects in this study was less compared to other studies and was limited to patients after CABG who participated in the phase II cardiac rehabilitation program only. This study only assessed changes in hsCRP values before and after the program without any follow-up regarding outcomes in the subjects. As we know, hsCRP also acts as a predictor of advanced cardiovascular events in patients who have been diagnosed with CHD. In this study there were still several subjects who did not participate in a complete rehabilitation program due to various causes such as the hospital was too far from their residence, lack of motivation, and lack of understanding of the importance of phase II cardiac rehabilitation programs.

Conclusion

There is a relationship between cardiac rehabilitation and hsCRPin patients who have undergone CABG. This study found a significant decrease in hsCRPafter subjects finished the program. Cardiac rehabilitation program not only improves laboratory components such as hsCRP and lipid profile, but also improves other metabolic parameters such as weight, BMI, waist circumference, and also improves the 6MWD and exercise capacity of patients after CABG. There is a negative correlation between hsCRP values and exercise capacity both before and after a rehabilitation program that is statistically significant.

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