



The Effects of Phase III Cardiac Rehabilitation in Serum and Salivary Hs-CRP and Anthropometric Measurements in Patients with Coronary Artery Disease

Boshra Jamshidpour, Behrouz Attarbashi Moghadam, Behnoosh Vasaghi-Gharamaleki
Iraj Mirzaii-Dizgah, Mostafa Nejatian

ABSTRACT

Aim: Cardiac rehabilitation is a key part in the treatment of coronary artery disease (CAD) by its anti-inflammatory effects. However, the effect of exercise training programs on salivary concentrations of high-sensitivity C-reactive protein (hs-CRP) in patients with coronary artery disease has not been well studied. The objective of this study was to evaluate the effect of phase III cardiac rehabilitation on serum and salivary levels of hs-CRP, in relation to the anthropometric measurements of obesity and the relationship between salivary and serum levels of hs-CRP in CAD male patients.

Materials and methods: Forty male volunteers (45-75 years) with CAD participated in 6 to 8 weeks of moderate intensity aerobic exercise training consisting of 45 minutes sessions of treadmill, stationary bicycle and arm ergometer. Anthropometric measurements of obesity, serum level of hs-CRP, stimulated and nonstimulated salivary level of hs-CRP were measured at the beginning, in the middle and at the end of exercise sessions.

Results: All anthropometric measurements increased ($p < 0.05$) following cardiac rehabilitation except waist-hip ratio. Serum hs-CRP level reduced by 36% independent to the anthropometric measurements changes. Stimulated and nonstimulated salivary hs-CRP level decreased 68 and 54%, respectively, after 24 sessions of cardiac rehabilitation. Nonstimulated salivary hs-CRP levels correlated to serum levels of hs-CRP at baseline and after 24 sessions ($p < 0.05$).

Conclusion: Phase III cardiac rehabilitation seems to be effective to improve serum and salivary hs-CRP concentrations independent of anthropometric measurements.

Clinical significance: Nonstimulated salivary hs-CRP measurement could be a surrogate for blood measurement of hs-CRP during cardiac rehabilitation in male patients with CAD.

Keywords: Saliva, High sensitivity C-reactive protein, Cardiac rehabilitation, Exercise training, Anthropometric measurements, Coronary artery disease.

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INTRODUCTION

Phase III cardiac rehabilitation is a crucial part in the treatment of coronary artery disease (CAD). Studies have demonstrated the benefits of cardiac rehabilitation and exercise training programs on coronary risk factors, including lipids, obesity indices, exercise capacity and cardiopulmonary fitness as well as significant reductions in overall cardiac morbidity and mortality.¹

Current thinking accords the inflammation is an important factor in the pathogenesis of atherosclerosis.² Among inflammatory markers high-sensitivity C-reactive protein (hs-CRP) has proved as one of the most powerful predictors for future cardiovascular risk.³ Elevated levels of hs-CRP have been independently shown to increase the risk of cardiovascular disease mortality and morbidity in both men and women.² Thus, inflammation becomes important purpose for treatment of CAD. Previous studies indicated that anthropometric measurements of obesity are important indicators of systemic inflammation, and are closely associated with raised levels of circulating CRP and other inflammatory mediators that are involved in the production of CRP from the liver, so anthropometric measures of obesity can lead to improve cardiovascular risk stratification of patients.^{4,5}

Aerobic exercise based phase III cardiac rehabilitation, is an effective nonpharmacological intervention for both primary and secondary prevention of CAD with several benefits including the reduction of inflammatory markers, namely CRP perhaps via its effect on abdominal fat and most importantly the reduction of cardiovascular mortality in revascularized CAD patients.⁶

Whereas, blood samples remain to be the most useful biological fluid to evaluate the pathophysiology of exercise, saliva is an effective alternative fluid that may indicate systemic alteration due to exercise.⁷

Salivary CRP levels have been used to assess whether CRP determination in saliva samples could be utilized as a way to detect inflammation, and as an alternative approach to evaluate disease risk and monitoring the response to treatment.⁸

Previous studies demonstrated that the plasma levels of hs-CRP are significantly decreased after exercise training program,^{3,9-12} suggesting that rehabilitation program may develop an anti-inflammatory reaction. However, reports showing the levels of hs-CRP in saliva before, during and after cardiac rehabilitation are lacking.

As an easily accessible fluid, saliva has many features such as the ease of collection, storage, transport and lower cost in abundant quantity for analysis. It does not clot, so lessening the manipulations required. The skin will be preserved intact by the collection of saliva instead of blood, so the dangers of blood collection do not apply to saliva.^{13,14} The concentrations of HIV and hepatitis antigens are less in saliva, so danger of infection from saliva is less than from blood.¹⁵

In the present study, we examined changes in the inflammatory status of male patients with CAD, assessed by serum and salivary concentrations of hs-CRP, in relation to the anthropometric measurements of obesity (body mass index (BMI), waist, hip circumference, waist-hip and waist-height ratio) after the exercise based cardiac rehabilitation. The correlation between salivary and serum levels of hs-CRP has been investigated too.

MATERIALS AND METHODS

Ethical and Human Subjects' Protection

The ethic committee of Tehran University of Medical Sciences (TUMS) approved the study protocol. All participants signed an approved written informed consent.

Study Population

Forty male patients with CAD were referred to the Cardiac Rehabilitation Department of Tehran Heart Center submitted to the study based on the exclusion criteria. These patients were revascularized by CABG 4 to 6 weeks ago. The following exclusion criteria were applied on these subjects: peripheral artery disease and/or orthopedic limitations, presence of pulmonary and renal comorbidity, metabolic disease (e.g. diabetes or thyroid disease), hypertension (systolic blood pressure >180 mm Hg or diastolic BP >100 mm Hg), unfavorable oral health conditions such as poor oral hygiene and periodontal diseases, complications during hospitalization. Patients were excluded if they

had the evidence of unstable angina pectoris, abnormal hemodynamic response or ischemic electrocardiogram changes, observed during exercise training. A general practitioner trained in cardiac rehabilitation determined the risk stratification of the patients according to the criteria of the American Association of Cardiovascular and Pulmonary Rehabilitation.¹⁶ Low and intermediate risk patients (45-75 years old) were considered. All cardiac related medication dosage was unchanged during the study period. Anthropometric measurements and salivary hs-CRP levels were evaluated at the beginning, in the middle and at the end of exercise sessions but serum hs-CRP concentrations were measured before and after the intervention treatments.

Anthropometric Measurements

Anthropometric measurements were taken in light clothing without shoes and in standing position. Weight was measured by a digital scale balanced (Omron model HN-283; Omron Corp., Japan). Height was measured against a wall chart. BMI (kg/m²) was calculated. Waist circumference was measured at the level of noticeable waist narrowing located approximately the mid-point between the lower border of the rib cage and the iliac crest, and the widest part of the gluteal muscles were measured as the hip circumference. The waist-hip and waist- height ratio were then calculated.

Saliva Collection

All patients were first informed about the saliva collection. The subjects were asked to fast for at least the period of one hour before to giving their saliva samples. The salivary collections were done in the morning between 7:30 and 10:30, while the subjects were in a sitting position. The subjects were asked to collect 2 to 4 ml of nonstimulated saliva in their mouths and to spit into a graded test tube. Thereafter, patients chewed a piece of natural gum for few minutes and then spat their stimulated whole saliva into another graded tube while continuing chewing the gum. Samples were kept in the refrigerator until delivered to the laboratory for processing, usually within 2 to 3 hours of collection. After centrifugation (8 min at 4,000 g), the supernatants were transferred to a microtube and kept frozen at -70°C until assay.

Blood Samples

The fasting patients were referred to the laboratory. three milliliter of venous blood was collected and was immediately analyzed. Serum and Salivary hs-CRP levels were measured by ELISA method using commercial kit (Accu-Bind Elisa Microwells, Monobind Inc., USA). Biomarkers assaying was performed as recommended detailed procedures by the own manufacturers.

Saliva and blood samples were obtained at least 24 hours after the last bout of exercise to avoid the acute effects of exercise while still representing the physiological effects of exercise.

Interventional Program

All patients completed the 24 sessions in an average of 8 weeks. Each exercise session consisted of endurance training on a cycle ergometer for 10 to 12 minutes, an arm ergometer for 8 to 10 minutes and treadmills for 10 to 15 minutes. Each step included warm up, training at constant workload, cool down, and post exercise recovery. In all sessions, electrocardiogram and heart rate were supervised by telemetry monitoring. At the beginning, exercise intensity was set at 40 to 55% of the individual maximum heart rate obtained in the prestudy graded exercise test, and then increased progressively to reach 70 to 85% maximum heart rate. Progressive updating of the exercise prescription was according to the patients' heart rate, tolerance level and cardiac symptoms.

STATISTICAL ANALYSIS

All data were expressed as mean \pm SD, and analyzed by SPSS, version 16.0. Subjects with missing data points were excluded. Normalized data were evaluated with the Kolmogorov–Smirnov test. The t-tests, repeated-measures analysis of variance with Bonferroni adjustments and Wilcoxon nonparametric tests depending on the normality of the variable distributions were used to compare significant changes in outcome variables. Correlation analyses were performed by the Spearman's method. All p-values are two-tailed. Values of $p < 0.05$ were considered statistically significant.

RESULTS

Among 60 men were included in the study, 40 patients completed the treatment period (mean age 59.05 ± 9.17 years). The baseline demographic and clinical characteristics of patients enrolled from August 2011 through December 2012 in this study are presented in Table 1. Among the patients, the use of anti-platelet drugs (100%) and anti-hyperlipidemia agents (90%) were more common. No changes in the medications doses were reported by the subjects throughout the study.

Eight weeks of rehabilitation led to significant improvement in maximum heart rate (8.7%), resting heart rate (13%) and functional capacity (42%).

No significant changes were registered for waist-hip ratio following cardiac rehabilitation ($p > 0.05$). BMI slightly increased ($p < 0.05$) after 12 (with a mean increase of 0.32 kg/m^2) and 24 sessions of exercise (with a mean increase of 0.66 kg/m^2). Waist, hip circumference and waist-height ratio increased ($p < 0.05$) after 24 seasons of exercise (Table 2). Serum hs-CRP levels reduced by 36, from 0.85 ± 1.00 to $0.54 \pm 0.79 \text{ mg/l}$ ($p < 0.05$), independent of changes in anthropometric measurements (Table 3).

The mean levels of hs-CRP concentration in the stimulated and non-stimulated saliva at the beginning, in the middle and at the end of exercise sessions are shown in Table 3. Stimulated and nonstimulated salivary hs-CRP concentrations decreased by 68 and 54% respectively after 24 sessions of cardiac rehabilitation ($p < 0.05$), whereas no significant change could be observed at the middle of study period.

Pearson correlation showed that nonstimulated salivary hs-CRP level is correlated to serum level of hs-CRP at

Table 1: Baseline characteristics of the study participants (n = 40)

Characteristics	Mean \pm SD or Number (percentages)
Weight (Kg)	77.53 \pm 9.02
Height (cm)	171.09 \pm 6.8
Age (years)	59.05 \pm 9.17
Medications:	
Aspirin or other antiplatelet drugs	
Anti-hyperlipidemia	40 (100%)
Beta-blockers	36 (90%)
Calcium-blockers	35 (87.5%)
Plavix	3 (7.5%)
Digoxin	1 (2.5%)
Diuretics	2 (5%)
ACE-inhibitors	13 (32.5%)
Nitrates	20 (50%)
	33 (82.5%)

ACE: angiotensin-converting enzyme

Table 2: Changes in body anthropometry measurements (n = 40) †

Variables	Session 0	Session 12	Session 24	p value (0 vs 12)	p value (0 vs 24)	p value (12 vs 24)
BMI (kg/m ²)	26.52 ± 3.00	26.87 ± 3.02	27.19 ± 3.04	0.00*	0.00*	0.00*
Waist circumference (cm)	99.23 ± 7.55	99.55 ± 7.10	100.26 ± 7.53	1	0.04*	0.02*
Hip circumference (cm)	103.06 ± 5.19	103.05 ± 5.05	103.97 ± 5.35	1	0.16	0.01*
Waist-hip ratio	0.963 ± 0.052	0.966 ± 0.047	0.964 ± 0.044	1	1	1
Waist-height ratio	0.581 ± 0.046	0.583 ± 0.044	0.587 ± 0.047	1	0.04*	0.03*
Functional capacity (METs)‡	7.37 ± 2.26	♣	10.47 ± 3.08		0.00*	
Resting heart rate (bpm)	83.17 ± 11.87	♣	71.78 ± 13.95		0.00*	
Maximum heart rate (bpm)	125.74 ± 15.43	♣	136.78 ± 16.95		0.01*	

†Data are presented as mean ± SD ; * : p < 0.05; ‡: METs: metabolic equivalent test; ♣: Not measured; 0 vs 12: session12 - 0, 0 vs 24: session 24 – 0, 12 vs 24: session 24 - 12

Table 3: Changes in serum and salivary concentration of hs-CRP (n = 40)†

Variables	Session 0	Session 12	Session 24	p value (0 vs 12)	p value (0 vs 24)	p value (12 vs 24)
Stimulated salivary hs-CRP (mg/l)	0.03 ± 0.05	0.02 ± 0.03	0.01 ± 0.01	-0.01	-0.02*	-0.01
Nonstimulated salivary hs-CRP (mg/l)	0.04 ± 0.04	0.03 ± 0.05	0.02 ± 0.02	-0.01	-0.02*	-0.01
Serum hs-CRP (mg/l)	0.85 ± 1.00	♣	0.54 ± 0.79		0.02*	

hs-CRP: high-sensitivity C-reactive protein; * : p < 0.05; 0 vs 12: session12 - 0, 0 vs 24: session 24 – 0, 12 vs 24: session 24 - 12

Table 4: Correlation coefficient between serum and salivary concentration of hs-CRP before and after cardiac rehabilitation (n = 40)

Before intervention treatment	Serum hs-CRP
Nonstimulated salivary hs-CRP	0.41*
Stimulated salivary hs-CRP	0.10
After intervention treatment	Serum hs-CRP
Nonstimulated salivary hs-CRP	0.70*
Stimulated salivary hs-CRP	0.14

*: p < 0.05 (tow tailed). hs-CRP: high-sensitivity C-reactive protein

baseline and following exercise training (r = 0.41, r = 0.70, respectively; p < 0.05). However, no correlation was found between serum and stimulated salivary level of hs-CRP at baseline and following exercise training (r = 0.10, r = 0.14, respectively) (Table 4).

DISCUSSION

In this study, we investigated the effects of exercise-based cardiac rehabilitation on serum and salivary concentrations of hs-CRP, in relation to the anthropometric measurements of obesity in male patients with CAD. Specifically we examined the relationship between salivary and serum levels of hs-CRP before and after phase III cardiac rehabilitation.

Two important findings of this study were that serum and salivary hs-CRP concentrations were reduced, independent of changes in body anthropometry (Table 3), and a correlation existed between nonstimulated salivary and serum hs-CRP levels before and after intervention (Table 4).

Several possible mechanisms have illustrated an anti-inflammatory effect of exercise training. Reduction of obesity especially abdominal obesity is one of these mechanisms. Some of the studies have observed general obesity^{1,17} and central obesity^{18,19} most strongly correlated with systemic inflammation as measured by hs-CRP. However, our findings of nonsignificant association between hs-CRP and anthropometric measures of obesity is in agreement with previous results showing that exercise training could mitigate the hs-CRP levels independent of changes in body weight or body mass index.^{2,9-11} In the present study, serum hs-CRP levels were reduced by 36% after aerobic exercise training without any changes in central obesity parameters, indicating that other mechanisms leading to the anti-inflammatory effect of exercise.

In this study BMI, waist and hip circumference and waist-height ratio were increased significantly but waist-hip ratio was not altered significantly by 8 weeks of exercise training (Table 2).



The importance of diet in reducing obesity has emphasized in the meta-analysis by Miller. They have expressed that the diet or combination of diet and exercise more than exercise alone has been more successful in achieving a considerable weight loss,²⁰ so exercise training alone probably could not be the main strategy in controlling of obesity and nutritional counseling has a major impact on weight loss. Before entering the exercise program, all patients of present study had enrolled in an education session and were well informed the composition of healthy diet but individualized dietary counseling were not offered. It seems that absence of weight loss due to an increased hunger response following the exercise training. Therefore, using individualized diet plan could help weight management while obtaining all of the benefits of exercise is expected.

There is a need to attention to the other health benefits of exercise including exercise capacity because several evidences indicate that weight loss is not certainly necessary to observe fundamental advantage. So, it has been reported that exercise training is associated with reduction of the incidence of CAD, cardiac morbidity and mortality by improvement in cardiopulmonary fitness, despite minimal or no change in BMI or body weight. Researches suggest that exercise capacity may be very important predictor of CHD and all-cause mortality.²¹⁻²³ Our results showed that aerobic exercise training improves functional capacity, resting heart rate and maximum heart rate significantly (Table 2), independent of anthropometric measures of obesity. These findings are in agreement with the results of previous studies reported that exercise training in cardiac rehabilitation program improves cardiopulmonary fitness of CAD patients, which may have not an influence on BMI.^{21,24} Thus, substantial health benefits can be achieved even in the absence of weight loss.

Several lines of evidence have continuously highlighted the role of hs-CRP in the process of atherosclerosis.²⁵ Several studies have evaluated the anti-inflammatory effect of exercise on serum CRP in patients with CAD, participating in cardiac rehabilitation.⁹⁻¹¹ The majority of these studies have reported that exercise training in coronary patients is associated with considerable reduction in serum hs-CRP levels. In the study by Millani et al reduction of serum hs-CRP concentrations was observed after 3-month exercise training and cardiac rehabilitation.⁹ Similar results were found in the study by Caulin-Glaser and Attarbashi Moghadam.^{10,11} In present study, we also found that serum hs-CRP levels decreased significantly following cardiac rehabilitation, as it has been reported previously. We found no study available evaluating the effects of exercise on salivary hs-CRP in patients with CAD. We assayed possible

change of the hs-CRP in stimulated and nonstimulated saliva, during exercised based cardiac rehabilitation. A significant decrease in stimulated and nonstimulated hs-CRP concentrations were observed following 24 sessions of exercise training that are similar to the results of serum samples.

Majority of acute phase proteins including hs-CRP are synthesized in the liver and then diffuse or are actively transported into saliva from the blood. Some of them are produced in the salivary glands.⁸ Since, a strong correlation between serum and nonstimulated salivary hs-CRP concentrations was observed before and after intervention, serum origin of hs-CRP is accepted. The association between serum concentrations of hs-CRP and stimulated saliva was not statistically significant. This might be due to foreign substances to stimulate the water of saliva, causing alteration the fluid PH and dilution in the concentration of proteins,²⁶ such as hs-CRP.

A limitation of this study is that information on changes of food intake was not collected, which may have affected on the body anthropometrics. In addition, Oral health status was not assessed. Some studies have reported that periodontal disease is associated with increased salivary and also serum CRP levels.⁸ We had not a control group because of ethical constraints.

CONCLUSION

Twenty-four sessions of exercise based phase III cardiac rehabilitation seem to be effective to improve exercise capacity, serum and salivary hs-CRP concentrations independent of anthropometric measurements in male patients with CAD.

CLINICAL SIGNIFICANCES

Nonstimulated salivary hs-CRP measurement could be a good surrogate for blood measurement to determine cardiovascular disease risk expressed by hs-CRP.

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ABOUT THE AUTHORS

Boshra Jamshidpour

Physical Therapist, Department of Physical Therapy, Tehran University of Medical Sciences, Iran

Behrouz Attarbashi Moghadam

(Corresponding Author)

Assistant Professor, Department of Physical Therapy, Tehran University of Medical Sciences, Iran, e-mail: attarbashi@tums.ac.ir

Behnoosh Vasaghi-Gharamaleki

Assistant Professor, Department of Basic Sciences-Rehabilitation Research Center, Iran University of Medical Sciences, Iran

Iraj Mirzaii-Dizgah

Associate Professor, Department of Physiology, AJA University of Medical Sciences, Iran

Mostafa Nejatian

Director of Cardiac Rehabilitation Department, Tehran Heart Center Tehran University of Medical Sciences, Iran