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Effect of cardiac rehabilitation on inflammation: A systematic review and meta-analysis of controlled clinical trials

Masoumeh Sadeghi[1], Hossein Khosravi-Broujeni[2], Amin Salehi-Abarghouei[3], Ramin Heidari[4], Gholamreza Masoumi[5], Hamidreza Roohafza[6]

Meta-analysis

Abstract

BACKGROUND: This systematic review and meta-analysis aimed to assess the effect of cardiac rehabilitation (CR) on serum C-reactive protein (CRP) as an indicator of the inflammatory state and predictor of recurrent cardiovascular events.

METHODS: PubMed, SCOPUS, Cochrane library, and Google Scholar databases were searched up to January 2014 for original articles which investigated the effect of CR on CRP among adult patients with previous cardiovascular events. The random effects model was used to assess the overall effect of CR on the variation in serum CRP levels.

RESULTS: In the present systematic review and meta-analysis, 15 studies were included. The analysis showed that CR might significantly reduce high-sensitivity CRP (hs-CRP) levels [Difference in means (DM) = -1.81 mg/l, 95% confidence interval (CI): -2.65, -0.98; P = 0.004). However, the heterogeneity between studies was significant (Cochran's Q test, P < 0.001, I-squared = 84.9%). To find the source of variation, the studies were categorized based on study design (quality) and duration. The negative effect was higher among studies which followed their participants for 3 weeks or less (DM = -2.75 mg/l, 95% CI: -3.86, -1.64; P < 0.001) compared to studies which investigated the effect of CR for 3-8 weeks (DM = -0.89 mg/l, 95% CI: -1.35, -0.44; P < 0.001) and those which lasted more than 8 weeks (DM = -1.71 mg/l, 95% CI: -2.53, -0.89; P < 0.001). There was no evidence of heterogeneity when the categorization was based on the follow-up period.

CONCLUSION: Both short- and long-term CR have resulted in improvement in serum hs-CRP levels. CR can be perceived as a beneficial tool to reduce inflammatory markers among patients with previous cardiac events.

Keywords: Cardiac Rehabilitation, Inflammation, C-Reactive Protein

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Introduction

Cardiovascular diseases (CVDs) are a group of disorders which effect the heart and blood vessels and are the leading cause of death, worldwide.[1] Based on the World Health Organization (WHO) reports, 17.3 million people (about 30% of global deaths) died due to CVDs in 2008, among which 7.3 and 6.2 million were reported to dye due to coronary heart disease (CHD) and stroke, the two major subclasses of CVDs, respectively. Inflammation is shown to be one of the important factors in the development and clinical course of most CVDs. Inflammation is actively involved in all levels of atherogenesis, from the initial lesions to the end-stage complications. Therefore, atherosclerosis is presently recognized as a low grade inflammatory vascular disease,[2] which maximizes after the cardiac events. Moreover, reducing the inflammatory state after the cardiovascular event might be of great importance. Inflammatory markers, including interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α) and particularly, C-reactive protein (CRP), are considered

1- Professor, Cardiac Rehabilitation Research Center, Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran
2- School of Medicine AND Menzies Health Institute, Griffith University, Southport, Queensland, Australia
3- Assistant Professor, Nutrition and Food Security Research Center AND Department of Nutrition, School of Health, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
4- Assistant Professor, Isfahan Cardiovascular Research Center, Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran
5- Associate Professor, Cardiac Anesthesiology Research Center, Chamran Heart Center Hospital, Isfahan University of Medical Sciences, Isfahan, Iran
6- Assistant Professor, Psychosomatic Research Center, Isfahan University of Medical Sciences, Isfahan, Iran
Correspondence to: Hamidreza Roohafza, Email: roohafza@crc.mui.ac.ir

as risk markers of CVDs.[3] The lipid-lowering therapy as a CVD risk-reducing strategy has also been reported to produce a parallel decrease in CRP. It has been shown that CRP concentrations decrease 15–50% with statin therapy.[4-6]

Cardiac rehabilitation (CR) has been defined as "comprehensive long-term services involving medical evaluation, prescribed exercise, cardiac risk-factor modification, health education, counseling, and behavioral interventions" by the United States Department of Health and Human Services (HHS) and the National Heart, Lung, and Blood Institute (NHLBI). CR has been shown to beneficially effect overall health and metabolic factors including inflammatory markers among patients who have experienced CVDs.[7-11] For instance, it has been shown that exercise training, as an important part of CR programs, might be more effective in reducing the inflammatory markers than standard treatments provided early after acute myocardial infarction.[12,13] Several studies have assessed the effect of CR on inflammatory markers including fibrinogen,[14,15] TNF-α,[16,17] and IL-6.[17,18] However, the majority of studies have selected high-sensitivity CRP (hs-CRP) levels as a widely acceptable marker of inflammation to assess the beneficial effects of CR on inflammatory state.[17,19-22] Furthermore, the use of serum CRP has been suggested as a predictor for CVDs and their recurrence.[23] Studies have led to conflicting results regarding the effect of CR on CRP levels. Some researchers have shown the beneficial effect of CR on CRP levels,[9,18,24,25] while others did not find the same results.[20] This is while the majority of published data are from low quality before-after trials,[8,20,24-26] and the parallel studies had not assessed the difference in the CRP level variation between their intervention group and controls.[9,13,17-19,22,27-29] To the best of our knowledge, no study has attempted to summarize published data about the effect of CR on CRP levels. As the clinical trials provide the most qualified data regarding this association, the present study aimed to systematically review the controlled clinical trials investigating the effect of CR on inflammatory markers in patients with CVDs, and if possible quantify their results and search for their possible sources of heterogeneity through a meta-analysis.

Materials and Methods

The online databases of PubMed, ISI Web of Science, Scopus, Science Direct, and Embase were searched for relevant English and non-English publications up to January 2014. Moreover, experts in this field were contacted and reference lists of the published papers were searched. The keywords used in the present search strategy consisted of those selected from the Medical Subject Headings (MeSH) database and other related non-MeSH terms. The non-MeSH terms consisted of 3 groups. The first group were keywords related to cardiac rehabilitation ("cardiac rehabilitation", "cardiovascular rehabilitation", "cardiopulmonary rehabilitation", OR "cardiac exercise", OR "cardiovascular exercise", OR "cardiopulmonary exercise", "rehabilitation", "cardiac rehab*", "pulmonary rehabilitation").

The second group were keywords related to cardiometabolic markers ["intercellular cell adhesion molecule (ICAM)", "vascular cell adhesion molecule (VCAM)", "adhesion molecule", "E-selectin", "fibrinogen", "white blood cell", "serum amyloid A", "cytokines", "erythrocyte sedimentation rate (ESR)", "total cholesterol (TC)", "inflammatory marker", "interleukin", "smoking", "inflammation", "inflammation mediators", "IL" OR "C-reactive protein", "c reactive protein", "CRP", "inflammatory", "inflammation", "tumor necrosis factor", "TNF", "interleukins", "CRP", "TNF-α", "cholesterol", "lipoproteins, high-density lipoprotein (HDL)", "lipoproteins, low-density lipoprotein (LDL)", "triglycerides", "glucose tolerance test (GTT)", "insulin", "blood glucose", "insulin resistance", "cholesterol", "lipoproteins, HDL", "lipoproteins, LDL", "triglycerides", "GTT", "insulin", "blood glucose", "insulin resistance", "LDL", "HDL", "triglyceride", "triacylglycerol (TG)", "TC", "GTT", "fast blood sugar (FBS)", " fasting blood glucose (FBG)", "fasting insulin", "FBS", "FBG", "insulin sensitivity", "blood sugar", "lipid profile", "serum lipid", "plasma lipid", "blood pressure", "hypertension", "blood pressure", and "hypertension"].

The third group consisted of keywords related to clinical trials ("intervention studies", "intervention", "controlled trial", "randomized", "randomized", "random", "randomly", "placebo", "assignment", "clinical trial", and "trial"). Databases were searched using keywords 1 in combination with 2 and 1 in combination with 3 and duplicate studies were removed. No filter or limitation was implemented while searching the mentioned databases.

To be included in the meta-analysis, a published study had to meet the following criteria: be an original article, a controlled clinical trial, and conducted in an adult human population, and having assessed the effect of CR on serum CRP levels.

As the majority of studies had reported CRP levels as their main outcome variable, in the present study, only these articles were included in the systematic review and meta-analysis. Data were

extracted on publication (the first author's last name, year of publication, and country of the studied population), number of individuals in the intervention and control groups, duration of the intervention, age, gender, and mean and standard deviation (SD) of inflammatory factors at baseline and after CR.

The mean and SD of CRP levels at baseline and after the intervention period was used to calculate the mean change in CRP levels and its corresponding SD which was included in the meta-analysis as an effect size (raw difference in means: DM) from each before and after study. The difference in CRP levels variation between intervention and control groups (DM) was also calculated and used as the effect size for controlled clinical trials. Summary mean estimates with their corresponding SDs were derived using the random effects model (method of DerSimonian and Laird),[30] which incorporates between-study variability. Subgroup analyses were performed to check for specific sources of heterogeneity. Sensitivity analysis was used to explore the extent to which inferences might depend on a particular study or group of studies. Publication bias was assessed by visual inspection of funnel plots.[31] In these funnel plots, the difference in mean CRP was displayed against the inverse of the square of the standard error (a measure of the precision of the studies). Funnel plots generally show a peak at the point where the studies with smaller standard errors are found which usually represents the point of the approximate true effect. Formal statistical assessment of funnel plot asymmetry was performed using Egger's regression asymmetry test and adjusted rank correlation test.[32] Reported P-values are from the intercept of the regression analysis, which provides a measure of asymmetry. In addition, Begg's adjusted rank correlation test was used.[32] Statistical analyses were carried out in Stata (version 11.2; StataCorp, College Station, TX, USA). *P* values of less than 0.05 were considered statistically significant.

Results

In the preliminary online search, 7418 studies were retrieved; about 7354 were excluded after reading titles or abstracts because they did not meet the inclusion criteria (Figure 1). Finally, 43 articles were found which had investigated the effect of CR on one of the inflammatory markers; among these, 15 articles had examined the association between CR and hs-CRP or CRP.[8,9,13,17-22,24-29] One of these 15 eligible studies had examined the effect of a very short-term period (1 session) of CR on hs-CRP levels in patients with ischemic heart disease (IHD).[21] As the objective of the present review was to assess the long-term effect of CR on CRP levels, this study was removed from the qualitative and quantitative synthesis. Moreover, a study performed by Hansen et al. was not included in the present review.[9] This study was a long-term follow-up (about 72 weeks) of two groups of patients randomly undergoing a 40-minute and 60-minute CR program for 7 weeks, and there was no intervention in the follow-up period.[9] Therefore,

13 articles were eligible to be included in the systematic review.[8,13,17-20,22,24-29] The characteristics of studies are presented in table 1. Studies were conducted in USA,[18,20,22] Italy,[8,24,26] South Korea,[17,27] Croatia,[13] Serbia,[28] Belgium,[29] Japan,[25] and Iran.[19] Among these studies, 5 were of lower quality because they had a before-after,[8,20,24-26] while others were parallel studies with control groups.[9,13,17-19,22,27-29] However, only in 2 of the parallel studies the patients were randomly assigned to intervention and control groups.[9,13] Although the study conducted by Hansen et al.[29] was a randomized controlled clinical trial, the intervention and control groups underwent 60 and 40 minutes of CR, respectively; therefore, the study was considered a before-after study which assessed the effect of the CR program on all its participants.

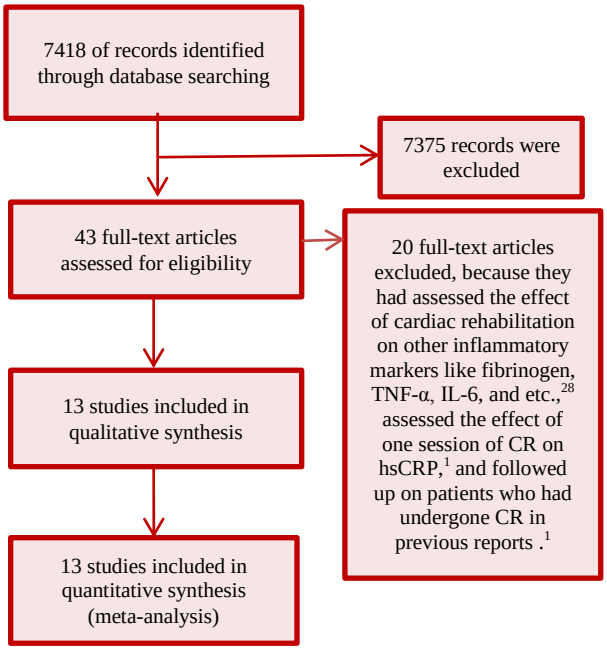

Figure 1. Flow chart for the study selection process
TNF-α: Tumor necrosis factor-α; IL-6: Interleukin-6; hs-CRP: High-sensitivity C-reactive protein; CR: cardiac rehabilitation

Table 1. Characteristics of studies evaluated the effect of cardiac rehabilitation (CR) on metabolic syndrome and/or its components

Author/year	Country	Subjects and gender	Mean Age (year)	Design	Intervention	Control	Duration	Outcome variable	Result
Fukuda et al.[25]	Japan	Patients with cardiovascular diseases (F: 6/M: 44)	61	Before-after	Aerobic bicycle exercise 2 or 3 times per week for 3–6 months	-	24 weeks	hs-CRP	hs-CRP levels decreased, but it was not statistically significant.
Ferratini et al.[24]	Italy	Patients after cardiac surgery (F: 68/M: 155)	67	Before-after	Up to 30 minutes of cycling 5 times a week at 70% maximal heart rate	-	3 weeks	hs-CRP	hs-CRP levels significantly decreased after CR program.
Cesari et al.[8]	Italy	Patients with acute coronary syndrome (F:20/M: 92)	58.2	Before-after	3 days/week of endurance training on a cycle-ergometer at 60–70% of VO2 level	-	4 weeks	hs-CRP	hs-CRP levels significantly decreased after CR program.
Aminlari et al.[19]	Iran	Patients with myocardial infarction (56 M/F)	62.7	Parallel (randomization was not mentioned)	Exercise training, education, and behavior modification therapy were performed 3 times per week. The exercise training included arm and leg ergometry and treadmills. Behavioral modifications were smoking cessation, healthy nutrition, hypertension control, and etc.	No intervention	8 weeks	CRP	CRP levels significantly decreased in the intervention group compared to controls.
Kim et al.[27]	South Korea	Patients with acute myocardial infarction (F:32/M: 109)	63.24	Parallel without randomization	Warm-up (10 minutes), exercise (30 minutes), and cool-down (10 minutes) The intensity of exercise was adjusted on a test result basis by calculation of heart rate reserve first, followed by the increased target heart rate from 40% to 85% of the value in phases	General training on exercise or risk factors management. instructed to maintain their own exercise	16 weeks	hs-CRP	The exercise group showed a significantly lower value of hs-CRP than the control group.
Rankovic et al.[28]	Serbia	patients with ischemic heart disease (F: 23/M:29)	60.22	Parallel (randomization was not mentioned)	Continual aerobic exercise for 45 minutes on a treadmill, room bicycle or walking The intensity of physical exercise was limited to the submaximal physical capacity at the level of 70-80% of maximal heart frequency at the stress test taken before cardiovascular rehabilitation. Physical exercise was applied 3 times a week.	Did not have physical training in the last 6 months, except for usual household activities.	3 weeks	hs-CRP	CRP levels decreased significantly in the exercise group compared to controls.

Table 1. Characteristics of studies evaluated the effect of cardiac rehabilitation (CR) on metabolic syndrome and/or its components (continue)

Author/year	Country	Subjects and gender	Mean Age (year)	Design	Intervention	Control	Duration	Outcome variable	Result
Cesari et al.[26]	Italy	Patients after cardiac surgery (F: 35/M: 51)	72.5	Before-after	Aerobic exercise at cycle ergometer and short lasting calisthenic exercises, with the resistance sequentially provided by the weight of single body segments and gentle, passive stretching involving all the main joints The training frequency was 6 times per week for a total of 12 training sessions.	-	15 days	hs-CRP	hs-CRP levels significantly decreased after CR program.
Lavie et al.[20]	USA	Patients with coronary heart disease (F:72/M:73)	65.37	Before-after	3 times per week group exercise and educational sessions, and individual exercise (between 1 and 3 times per week) on non-rehabilitation days	-	12 weeks	hs-CRP	hs-CRP levels significantly decreased only among obese participants but not among lean subjects.
Kim et al.[17]	South Korea	Patients with coronary artery disease (F:11/M: 28)	50.08	Parallel (randomization was not mentioned)	Supervised exercise under prescription based on symptom-limited treadmill exercise test at hospital lasted 6 weeks + a home based and self-managed exercise lasting 8 weeks The exercise: warm-up, 30- to 40-min exercise on a treadmill or bicycle ergometer, and a cool-down	followed up with standard care as outpatients	14 weeks	hs-CRP	hs-CRP significantly decreased only among patients undergoing cardiac rehabilitation compared to controls.
Hansen et al.[29]	Belgium	Patients with coronary artery disease (F: 25/M: 109)	63.15	before-after	60 or 40 minutes of exercise (42% on the treadmill, 33% on the cycle ergometer, and 25% on the arm cranking device)		7 weeks	CRP	hs-CRP levels decreased in both exercise groups.
Balen et al.[13]	Croatia	Patients with acute myocardial infarction (F: 16/M: 44)	60	Randomized controlled clinical trial	45-minute aerobic activity on a cycle-ergometer and 30-minute organized program of supervised walking on a standardized track	standard care	3 weeks	hs-CRP	hs-CRP significantly decreased in both groups, but after the intervention, values were significantly lower among patients with cardiac rehabilitation.

Table 1. Characteristics of studies evaluated the effect of cardiac rehabilitation (CR) on metabolic syndrome and/or its components (continue)

Author/year	Country	Subjects and gender	Mean Age (year)	Design	Intervention	Control	Duration	Outcome variable	Result
Shin et al.[18]	USA	patients with coronary artery disease after percutaneous coronary intervention (F: 11/M: 28)	56.58	Parallel	Cardiac rehabilitation following hospital discharge and 8 weeks of home stay exercise plus statin therapy All subjects were prescribed daily lipid lowering medication consisting of 100 mg aspirin and 75 mg clopidogrel throughout the experimental period.	80 mg daily of fluvastatin	14 weeks	hs-CRP	hs-CRP significantly decreased in both groups but after intervention values were significantly lower among patients with cardiac rehabilitation.
Milani et al.[22]	USA	Patients with coronary heart disease (F:75/M: 202)	66.27	Parallel	Patients received formalized exercise instruction and met 3 times per week for group exercise classes, and were encouraged to exercise on their own (1 to 3 times per week) in between sessions.	Did not have cardiopulmonary exercise tests.	12 weeks	hs-CRP	hs-CRP levels significantly decreased only among patients with cardiac rehabilitation.

F: Female, M: Male; hs-CRP: High-sensitivity C-reactive protein

Results of meta-analysis: Of the 15 eligible article for the systematic review, 2 studies did not report data about baseline and post-intervention serum CRP levels;[19,25] These data could not be obtained even after contacting the authors twice through email, 1 week apart. Therefore, 13 studies were included for the quantification of the effect of CR on serum CRP levels.[8,9,13,17,18,20-22,24,26-29] In total, 992 adult participants with CVDs were included in the current analysis. The analysis showed that CR significantly reduces hs-CRP levels [DM = -1.81 mg/l, 95% confidence interval (CI): -2.65, -0.98; P = 0.004). However, the heterogeneity between studies was significant (Cochran's Q test, P < 0.001, I-squared = 84.9%) (Table 2).

Table 2. Forest plot demonstrating weighted mean differences with 95% confidence interval (CI) for all eligible studies investigating the effects of cardiac rehabilitation on C-reactive protein/high-sensitivity C-reactive protein levels grouped by study designs using random effects model

Study	DM (95% CI)
Before-after studies	
Lavie et al.[20] (obese)	-3.40 (-4.94, -1.86)
Lavie et al.[20] (lean)	-1.00 (-2.60, 0.60)
Hansen et al.[29]	-0.80 (-1.66, 0.06)
Cesari et al.[26]	-0.20 (-6.36,5.96)
Ferratini et al.[24]	-2.90 (-3.15, -2.65)
Cesari et al.[8]	-0.93 (-1.47, -0.39)
Subtotal (I-squared = 92.0%, P < 0.001)	-1.74 (-2.93, 0.55)
Parallel studies with no randomization	
Milani et al.[22]	-2.40 (-15.04, 10.24)
Shin et al.[18]	-1.49 (-3.48, 0.50)
Kim et al.[17]	-1.00 (-2.68, 0.68)
Rankovic et al.[28]	-1.51 (-3.11, 0.09)
Kim et al.[27]	-1.50(-2.85, 0.15)
Subtotal (I-squared = 0.0%, P = 0.991)	-1.39 (-2.19, 0.59)
Randomized clinical trial	
Balen et al.[13]	-4.50 (-6.63, -2.37)
Subtotal (I-squared = 0%, P < 0.001)	-4.50 (-6.63, -2.37)
Overall (I-squared = 84.9%, P < 0.001)	-1.81 (-2.65, -0.98)

DM: Difference in means; CI: Confidence interval

To find the source of variation, the studies were categorized based on their design (quality) and duration. When categorizing studies based on their design, the significant reducing effect of CR was observed in before-after studies (DM = -1.74 mg/l, 95% CI: -2.93, -0.55; P = 0.001), parallel studies (DM = -1.39 mg/l, 95% CI: -2.19, -0.59; P < 0.001), and randomized controlled (DM = -4.5 mg/l, 95% CI: -6.63, -2.37; P < 0.001) clinical trials. The heterogeneity was still significant among before-after studies (Cochran's Q test, P < 0.001, I-squared = 92%), while there was no evidence of heterogeneity between parallel studies (Cochran's Q test, P = 0.990, I-squared = 0.0%). Studies were also categorized based on their follow-up period (Table 3). Although, the reducing effect was statistically significant for all these subgroups, the negative effect was higher among studies which followed their participants for 3 weeks or lower (short follow-up period) (DM = -2.75 mg/l, 95% CI: -3.86, -1.64; P < 0.001) compared to studies which investigated the CR effect for 3-8 weeks (middle follow-up period) (DM = -0.89 mg/l, 95% CI: -1.35, -0.44; P < 0.001) and those which lasted more than 8 weeks (long follow-up period) (DM = -1.71 mg/l, 95% CI: -2.53, -0.89; P < 0.001). Although the I-squared showed a moderate heterogeneity among studies with short follow-up periods (48.2%), Cochran's Q test did not provide a significant evidence of heterogeneity (P = 0.122). The heterogeneity was not significant for studies with middle- (Cochran's Q test, P = 0.80, I-squared = 0.0%) and long-term follow-up periods (Cochran's Q test, P = 0.290, I-squared = 19.4%).

Table 3. Forest plot demonstrating weighted mean differences with 95% confidence interval (CI) for all eligible studies investigating the effects of cardiac rehabilitation on C-reactive protein/high-sensitivity C-reactive protein levels grouped by study follow-up period using random effects model

Study	DM (95% CI)
Short follow-up period	
Balen et al.[13]	-4.50 (-6.63, -2.37)
Rankovic et al.[28]	-1.51 (-3.11, 0.09)
Cesari et al.[26]	-0.20 (-6.36,5.96)
Ferratini et al.[24]	-2.90 (-3.15, -2.65)
Subtotal (I-squared = 48.2%, P = 0.122)	-2.75 (-3.86, -1.64)
Middle follow-up period	
Hansen et al.[29]	-0.80 (-1.66, 0.06)
Cesari et al.[8]	-0.93 (-1.47, -0.39)
Subtotal (I-squared = 0.0%, P = 0.801)	-0.89 (-1.35, -0.44)
Long follow-up period	
Milani et al.[22]	-2.40 (-15.04, 10.24)
Shin et al.[18]	-1.49 (-3.48, 0.50)
Lavie et al.[20] (obese)	-3.40 (-4.94, -1.86)
Lavie et al.[20] (lean)	-1.00 (-2.60, 0.60)
Kim et al.[17]	-1.00 (-2.68, 0.68)
Kim et al.[27]	-1.50(-2.85, 0.15)
Subtotal (I-squared = 19.4%, P = 0.287)	-1.71 (-2.53, 0.89)
Overall (I-squared = 84.9%, P < 0.001)	-1.81 (-2.65, -0.98)

DM: Difference in means; CI: Confidence interval

In a sensitivity analysis, it was found that the effect of CR on CRP levels was not substantially modified by the result of a certain study. Although a slight asymmetry was seen in Begg's funnel plot, no evidence of publication bias was found using asymmetry tests (Egger's test, P = 0.192, Begg and Mazumdar test, P = 0.170) (Figure 2).

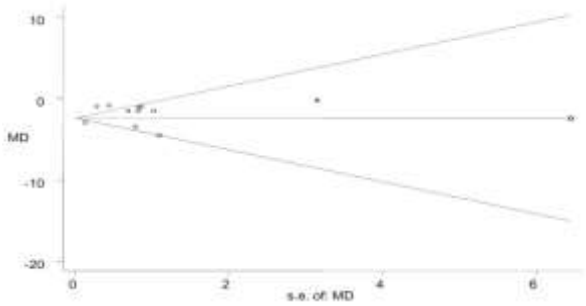

Figure 2. Begg's funnel plot with pseudo 95% confidence interval (CI) of the difference in means versus the standard errors of the difference in means for studies investigating the effect of cardiac rehabilitation on C-reactive protein/high-sensitivity C-reactive protein (b)
MD: Mean difference

Discussion

The systematic review and meta-analysis on clinical trials revealed the significant reducing effect of CR on serum hs-CRP levels. The analysis also showed that CR beneficially affects inflammation both in a short and long period of time. Therefore, CR might reduce the risk of CVDs recurrence not only through its beneficial effects on the lipid profile, but also through its effect on the inflammatory state. To the best of our knowledge, this is the first systematic review and meta-analysis assessing the effects of CR on inflammatory markers.

CRP, as a liver-derived molecule that is increased in inflammatory states, rapidly increases within hours after tissue injuries like CVDs.

Since CVD is at least in part an inflammatory process, CRP has been investigated in the context of arteriosclerosis and subsequent vascular disorders. CRP is recommended as a predictive laboratory marker for CVD risk in patients with high susceptibility to CVDs or their recurrence.[33] CRP has been shown to have some advantages as a marker: (1) It is a stable marker; (2) It does not have clinically significant circadian variation; and (3) It's measurement is easy and reliable.[34] Therefore, decreasing the inflammatory state markers including CRP levels might help patients to decrease the risk of recurrence of CVDs.

Aerobic exercise, as an adjunct to pharmacological therapy in patients with chronic heart failure and CAD, is known to improve peripheral vascular function and skeletal muscle abnormalities. Although exercise causes stress-induced up-regulation of endothelial nitric oxide synthase (eNOS),[35] it is supposed that the modification of inflammatory mediators through exercise reverses peripheral vascular endothelial dysfunction.[16] The present study results are in line with the previous reports suggesting that CR improved the inflammatory markers of patients experiencing CVDs.[8,13,19,22] Therefore, CR must be considered as an important strategy adjacent to conventional therapy used for patients experiencing cardiac events.

Some limitations must be considered while interpreting the present results. The effect of CR on CRP levels was studied because it is an acceptable marker for inflammation and also might be used as a predictor of cardiovascular events. Furthermore, the majority of published studies had selected the same marker to assess the inflammatory state. A limited number of studies were found which had used other inflammatory markers like TNF-α and interleukins.[16-18] Further studies on the effect of CR on other inflammatory markers are highly recommended in order to determine whether CR has the same beneficial effects. In addition, it has been proposed that the beneficial effect of CR might be because of its negative effect on body fat and obesity. Lavie et al. showed that the beneficial effect of CR on CRP levels is only significant in obese patients with CHD.[20] it has also been proposed that circulating hs-CRP and inflammatory cytokines are in relation with obesity among healthy subjects.[36] In the present review, there was only one study which had separately examined the effect of CR on hs-CRP levels among obese and lean participants.[20] Furthermore, the majority of eligible studies did not report the effect of CR on weight or BMI variation; therefore, the association between obesity or body fat and CRP levels variation could not be explored.

In conclusion, the present systematic review provides strong evidence of the beneficial effect of CR on the inflammatory state of patients with CVDs. It is highly recommended that further studies be conducted to explore whether CR affects other inflammatory markers and how dependent the changes in inflammatory markers

as a result of CR are on the magnitude of the change in body composition.

Conclusion

Both short- and long-term CR program have resulted in improvement in serum hs-CRP levels. CR can be perceived as a beneficial tool to reduce inflammatory markers among patients with previous cardiac events. It is highly recommended that further studies be conducted to explore whether CR affects other inflammatory markers and how dependent the changes in inflammatory markers as a result of CR are on the magnitude of the change in body composition.

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Conflict of Interests

Authors have no conflict of interests.

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