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Research Article

Effects of Exercise-Based Cardiac Rehabilitation on Cardiac Inflammatory Markers in Coronary Artery Disease - A Narrative Review

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Abstract
Background: *Coronary artery disease (CAD) is closely linked to chronic inflammation, with biomarkers such as hsCRP, IL-6, and copeptin playing key roles in disease progression. Cardiac rehabilitation (CR), particularly exercise-based programmes, has shown promising results in reducing these inflammatory markers and improving cardiovascular outcomes. This review examines how CR influences inflammatory cardiac markers and supports long-term cardiovascular health.*
Objective: *To evaluate the impact of cardiac rehabilitation on inflammatory cardiac markers in CAD patients and assess how different exercise protocols influence these outcomes. The goal is to identify which biomarkers respond most consistently to CR and how these changes correlate with clinical improvements.*
Method: *A Narrative review was conducted using studies involving exercise-based CR in CAD patients. Included studies measured biomarkers such as hsCRP, IL-6, and copeptin. Both randomised controlled trials and observational studies were considered.*
Results: *12 RCT's were included in the study that suggested that there is reduction in inflammatory biomarkers in CAD patients after exercise training.*
Conclusion: *Exercise based cardiac rehabilitation significantly reduces inflammatory markers in CAD patients, with improvements observed across various exercise types and durations. HIIT and longer programmes show enhanced effects.*
Keywords: *Cardiac rehabilitation, coronary artery disease, inflammatory markers, exercise therapy.*

Introduction

Coronary Artery Disease (CAD), also known as ischemic heart disease, is a chronic condition caused by the progressive narrowing or blockage of the coronary arteries, usually due to atherosclerosis.[1] As the primary vessels that supply oxygenated blood to the heart muscle, impairment of these arteries can lead to reduced myocardial perfusion.[2] Roughly **32–47 million** are currently living with CAD, but this is expected to **rise sharply** over the coming decades due to the increasing incidence of risk factors like hypertension, diabetes, obesity, and dyslipidemia. CAD prevalence has reportedly increased by **300% over the past four decades,** with the disease spreading faster in urban areas and in economically transitioning states.[3]

The term 'biomarkers' refers to the biological indicators for disease occurrence, while risk factors

indicate cause-and-effect relationships.[4] Natriuretic peptides, including B-type natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP), are cardiac hormones secreted mainly by the ventricles in response to increased wall stretch and pressure overload. They play a central role in regulating fluid balance, vascular tone, and cardiac remodelling, and are widely recognised as sensitive biomarkers of cardiac stress and prognosis. These changes reflect improved ventricular efficiency, reduced hemodynamic strain, and better adaptation to physical activity, highlighting the importance of natriuretic peptides in assessing the therapeutic impact of rehabilitation programs.[5,6] C-reactive protein (CRP) is an acute-phase protein produced by the liver in response to systemic inflammation and tissue injury, and it serves as one of the most reliable circulating biomarkers for cardiovascular risk assessment. In patients with coronary artery disease (CAD), elevated CRP levels are strongly associated with a higher incidence of atherosclerotic progression, plaque instability, and adverse cardiovascular outcomes.[7]

Interleukin-6 (IL-6) is a key inflammatory cytokine that plays a central role in the pathogenesis of ischemic heart disease. It is released by various cells, including macrophages and endothelial cells, in response to tissue injury and oxidative stress. Elevated IL-6 levels are associated with plaque instability and adverse cardiovascular outcomes.[8] While acute exercise may temporarily raise IL-6 concentrations, regular aerobic training tends to modulate its expression, contributing to reduced systemic inflammation and improved vascular function[9] .Apo-Lipoprotein A1 is one of the most abundant Apolipoproteins in plasma and is a major component of the cardio-protective HDL[10,11]. Homocysteine (Hcy) originates from the metabolism of the essential amino acid methionine, after a remethylation process catalysed by methylene tetrahydrofolate reductase enzyme, or from transsulfuration to form cystathionine. Homocysteine is characterised by its atherogenic, oxidant and inflammatory effects. These effects may be the result of promoting coagulation, endothelial damage, LDL oxidation and DNA hypomethylation[12,13.] Homocysteine is known as an independent risk factor for atherosclerosis.

Cardiac Rehabilitation refers to coordinated, multifaceted interventions designed to optimise a cardiac patient's physical, psychological, and social functioning, along with stabilising, slowing, or even reversing the progression of the underlying atherosclerotic processes, thereby reducing morbidity and mortality. (AHA)**.** CR has been shown to beneficially affect overall health and metabolic factors, including inflammatory markers, among patients who have experienced CVDs.[14] 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.[15] It has proven benefits, including reduced cardiovascular mortality, improved quality of life, and enhanced exercise capacity.[16] It also modifies key risk factors, with training volume playing a greater role than intensity.f[17] It has also been shown to reduce homocysteine (Hcy) and increase apolipoprotein A1 (ApoA1) in conditions like stable angina, contributing to slowed disease progression and improved outcomes.[18]

Existing research on the effects of Exercise Training on inflammatory markers in CAD patients varies in methodology, sample size, and outcome measures. A comprehensive review is needed to synthesise current findings and identify gaps in knowledge. Moreover, inflammatory markers such as hsCRP and IL-6 are strongly associated with cardiovascular risk. Hence, understanding how Exercise training modulates these biomarkers can enhance risk stratification and treatment personalisation. It may serve as a non-pharmacological adjunct to standard medical therapy, offering molecular-level benefits that go beyond symptom relief and physical conditioning. By conducting a thorough literature review, this study aims to provide a consolidated overview of the impact of Exercise Training on inflammatory biomarkers in CAD and support the development of more targeted rehabilitation strategies.

Literature Review

Table 1: Summary of articles with study design and outcomes.

Sr No.	Author	Title	Year	Study Design	Conclusion
1	Juliano Lara ,Carlos Vicente Serrano et al.[19]	Acute and chronic effects of exercise on inflammatory markers and B-type natriuretic peptide in patients with coronary artery disease	2011	Randomised control trial	The study found that acute and chronic effects of exercise on the inflammatory marker B-type natriuretic peptide (BNP) in patients. Acute bouts of exercise temporarily elevated markers such as CRP and VCAM-1; long-term training significantly reduced baseline levels of these biomarkers. indicating improved cardiac function, reinforces the anti-inflammatory and cardioprotective benefits of sustained cardiac rehabilitation.
2	Richard V. Milani, Carl J. Lavie et al.[20]	Reduction in C-Reactive Protein Through Cardiac Rehabilitation and Exercise Training	2004	Randomised control trial	A study conducted on 235 subjects with CAD showed that cardiac rehabilitation significantly reduced hsCRP levels in CAD patients, demonstrating its anti-inflammatory and cardiovascular risk-lowering benefits.
3	J. Cwikiel , Ingebjørg Seljeflot, et al.[21]	Effect of strenuous exercise on mediators of inflammation in patients with coronary artery disease	2018	Randomised controlled trial	The study conducted on 74 patients demonstrated that Strenuous exercise briefly increases inflammation in CAD patients. Moderate, supervised cardiac rehabilitation promotes long-term reductions in inflammation through beneficial adjustments in immune system activity.
4	Christella S. Alphonsus, Pooveshni	The role of cardiac rehabilitation using	2019	Randomised controlled trial	A study conducted on 16 individuals, who underwent Exercise-based cardiac rehabilitation, which

	Govender. et al.[22]	Exercise to decrease natriuretic peptide levels in non-surgical patients			significantly reduced natriuretic peptide levels in non-surgical patients within 12 weeks, suggesting improved cardiac function and potential reduction in morbidity and mortality risks
5.	Richard Yang , HongchaoZheng , et al.[23]	Cardiac Rehabilitation with Targeted Intensity Improves Cardiopulmonary Functions Accompanying with Reduced Copeptin Level in Patients with Coronary Artery Disease	2020	Randomised Controlled Trial	Cardiac rehabilitation programs with targeted intensity improved peak oxygen uptake and reduced copeptin levels, indicating enhanced cardiopulmonary function and reduced cardiovascular stress in coronary artery disease patients.
6	Catarina Goncalves , Armando Raimundo.et al.[24]	Effects of High-Intensity Interval Training vs. Moderate-Intensity Continuous Training on Body Composition and Blood Biomarkers in Coronary Artery Disease Patients	2024	Randomised Controlled Trial	The study demonstrates that both HIIT and MICT effectively improve body composition, blood pressure, and cardiovascular biomarkers like CRP and interleukins in coronary artery disease patients. However, HIIT yielded greater reductions in inflammation and better lipid profile improvements, highlighting the added value of intensity-tailored exercise in optimizing cardiac rehab outcomes

7	Claes Held, Harvey D. White.et al[25]	Inflammatory Biomarkers Interleukin-6 and C-Reactive Protein and Outcomes in Stable Coronary Heart Disease: Experiences From the STABILITY (Stabilization of Atherosclerotic Plaque by Initiation of therapy)	2025	Randomised controlled trial	The Stability trial demonstrated that interleukin-6 is a strong and independent predictor of adverse outcomes in patients with stable coronary artery disease, Evidence from cardiac rehabilitation research indicates that structured exercise and lifestyle interventions can reduce both IL-6 and CRP, cardiopulmonary capacity, and overall cardiovascular health
8	Agustín Manresa Rocamora , Susana Lopes.et al[26]	Effects of exercise-based cardiac rehabilitation on inflammatory biomarkers in patients with cardiovascular disease	2022	Randomised controlled trial	The study suggested that aerobic rehabilitation reduced the key inflammatory biomarkers in CVD patients, especially CRP and TNF-alpha. Results proved that shorter, exercise-only interventions had stronger anti- inflammatory benefits
9	Xing Miao, Hui Jiang. et al.[27]	Randomised trial of early exercise rehabilitation and its effects on patients with acute coronary syndrome	2024	Randomised controlled trial	This randomised study included 200 patients with acute coronary syndrome to assess early exercise rehabilitation. The intervention suggested that there was a significant reduction in levels of troponin and improved fasting glucose levels and depression scores, demonstrating cardiac rehabilitation's beneficial impact on inflammatory and metabolic biomarkers in CAD.

10	Muhammad Ferhat E , Zainal Safriet al.[28]	Interleukin-6 Reduction as a Predictor of Functional Capacity Improvement after Phase II Cardiac Rehabilitation Programme in Coronary Artery Bypass Surgery Patients	2024	Randomised controlled trial	The study concludes that reduced Interleukin-6 levels following Phase II cardiac rehabilitation in post-CABG patients showed improved functional capacity, supporting IL-6 as a biomarker for rehabilitation effectiveness and cardiovascular recovery.
11	Badai B. Tiksnadi, Melisa Aziz. Et al[29]	Functional Capacity improvement related to inflammatory marker reduction after phase II Cardiac rehabilitation programme in coronary artery bypass surgery patients	2019	Randomised controlled trial	In this study, 37 post-revascularization coronary artery disease patients undergoing phase II cardiac rehabilitation. The program significantly improved functional capacity and reduced hs-CRP levels, demonstrating cardiac rehab's dual benefit of enhancing fitness and lowering inflammatory biomarkers
12	Sherin H. M. Mehaniet al.[30]	Novel molecular biomarkers' response to a cardiac rehabilitation programme in patients with ischaemic heart disease	2018	Randomised controlled trial	The study found that cardiac rehabilitation significantly reduced serum homocysteine, increased apolipoprotein A1, and improved peak VO_2 and muscle strength, showing its dual benefit in enhancing functional capacity and modulating key molecular biomarkers in CAD patients.
13	Malene Munk Jørgensen, Annemette Krintel Petersen[31]	Exercise-Based Cardiac Rehabilitation Reduces Key Inflammatory Biomarkers in Atherosclerosis	2018	Randomised controlled trial	This study showed that a 12-week exercise-based cardiac rehab program led to greater short-term reductions in IL-6, hsCRP, and pro-inflammatory monocytes than an 8-week program, suggesting sustained exercise may help preserve anti-inflammatory benefits over time.

14	Ehud Goldhammer,T, Alon Tanchilevitch. et al.[32]	Exercise training modulates cytokine activity in coronary heart disease patients	2005	Randomised controlled trial	This study involved 28 coronary artery disease patients who completed a 12-week aerobic exercise program. Cardiac rehabilitation significantly reduced pro-inflammatory biomarkers—CRP, IL-1, IL-6, INF-γ—and increased anti-inflammatory IL-10, highlighting its immunomodulatory benefits in CAD management
15	Claudia Walthera, Sven Mo¨bius-Winkler, et al. [33]	Regular exercise training compared with percutaneous intervention leads to a reduction of inflammatory markers and cardiovascular events in patients with coronary artery disease	2007	Randomised controlled trial	This randomised trial included 101 male patients with stable coronary artery disease, comparing regular exercise training to percutaneous coronary intervention showed, exercise-based Cardiac rehabilitation significantly reduces hs-CRP and IL-6 levels and improved cardiovascular outcomes.
16.	Lene Rorholm Pedersen, , Rasmus Huan Olsen.et al.[34]	Effects of 1 year of exercise training versus combined exercise training and weight loss on body composition, low-grade inflammation and lipids in overweight patients with coronary artery disease	2019	Randomised controlled trial	This randomised trial included 70 overweight coronary artery disease patients aged 45–75. Exercise, which included along with weight loss, improved VO_2 peak, lipid profiles, and reduced inflammatory biomarkers—CRP, suPAR, and TNF-α—highlighting cardiac rehab's multifaceted benefits.

Study Design

Search Method and Eligibility Criteria

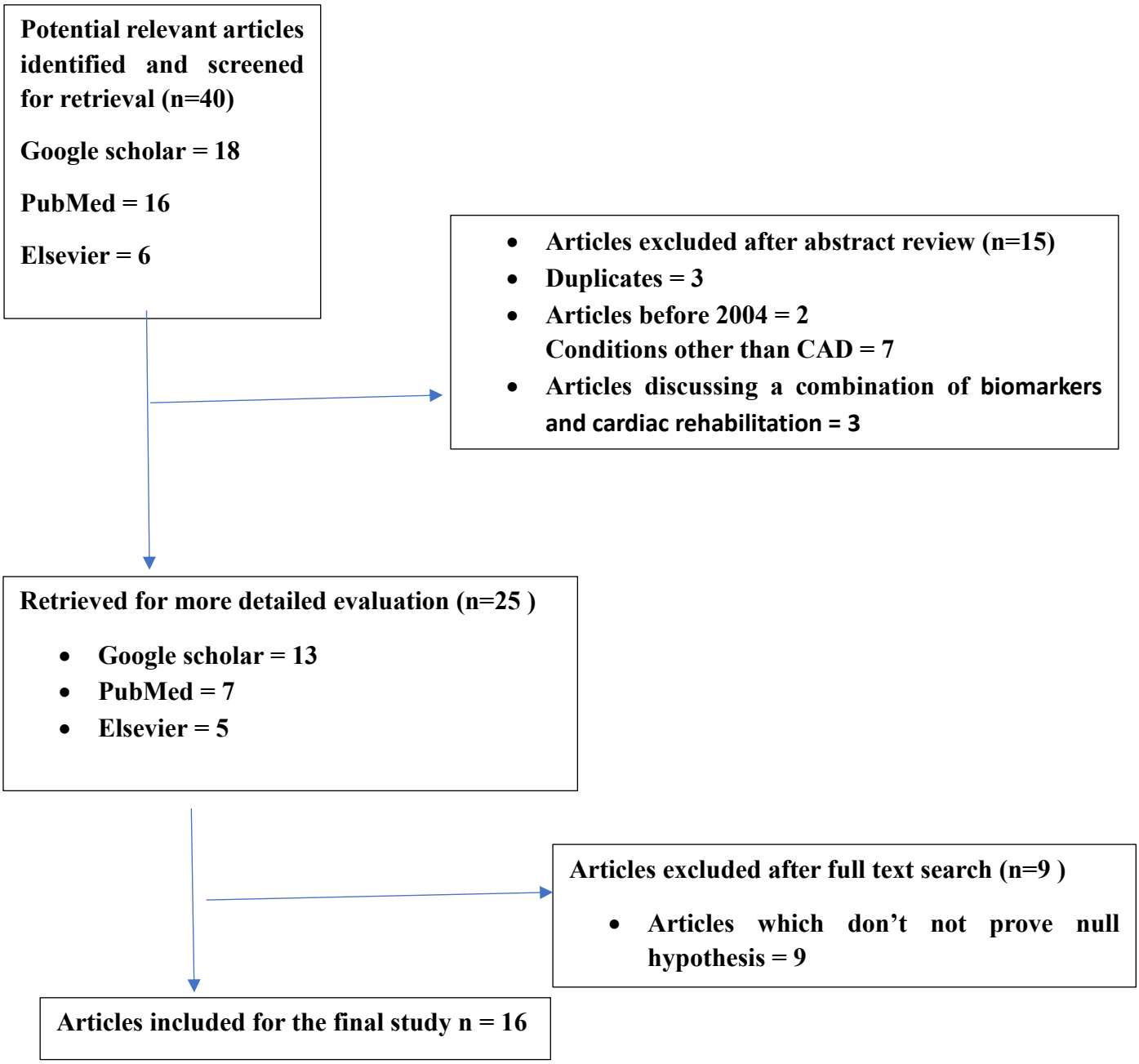
An extensive literature search was conducted using databases such as PubMed, Google Scholar, and Elsevier. The review process began by screening the titles of all identified references and removing duplicates or clearly irrelevant studies. Abstracts of the remaining articles were then reviewed to assess relevance based on study type, participant characteristics, objectives, interventions, and language. Relevant studies were categorised independently and assessed in full text. Only studies

evaluating the effects of exercise-based cardiac rehabilitation on inflammatory biomarkers in coronary artery disease were included in the final analysis.

Sample Size: A total of 46 articles were identified using keywords such as cardiac rehabilitation, coronary artery disease, inflammatory biomarkers, CRP, and NTP. After applying the inclusion and exclusion criteria, 16 articles were selected for final review. **Inclusion Criteria**: Articles discussing exercise-based cardiac rehabilitation, studies involving coronary artery disease patients; and studies reporting changes in inflammatory biomarkers were included in the study. **Exclusion Criteria**: Articles published before 2004; studies not involving CAD patients; articles focusing on non-exercise interventions; non-English publications; and abstracts, editorials, or incomplete reports were excluded from the study.

Methodology

Flow chart of article selection process



Discussion

Almost 80% of CAD and atherosclerosis-related morbidity and mortality can be prevented by modifying behaviours like physical inactivity. However, exercise is often under-prescribed to CAD patients, reducing inflammatory burden through CR has direct implications for secondary prevention and recurrent event reduction. Sherin H. M. Mehani et al conducted a comprehensive analysis and examined how molecular biomarkers respond to cardiac rehabilitation (CR) in patients with ischaemic heart disease. The study emphasised that exercise training improves not only functional capacity and cardiovascular outcomes but also modulates biomarkers linked to inflammation, oxidative stress, and endothelial function. Also, growing evidence highlights that biomarkers such as high-sensitivity C-reactive protein (hs-CRP) and interleukin-6 (IL-6) reflect physiological adaptation during rehabilitation. These changes indicates reduced inflammation and improved vascular health, which are vital for long-term IHD management. However, further research is needed to establish standardised biomarker panels for evaluating CR efficacy. Larger, multicenter studies with extended follow-up are essential to validate these findings.[30]

The influence of exercise-based cardiac rehabilitation (ECR) on inflammatory biomarkers in patients with ischaemic heart disease (IHD) has been explored through a dose-response study comparing an extended 12-week ECR programme with a conventional 8-week programme. Study. That suggested a 12-week programme led to significantly greater reductions in key inflammatory markers such as interleukin-6 (IL-6), high-sensitivity C-reactive protein (hsCRP) at the end of rehabilitation. This suggests that longer-duration ECR may offer enhanced anti-inflammatory effects, contributing to vascular healing and reduced atherosclerotic risk. However, the study found no sustained differences at 6-month and 1-year follow-ups, indicating that long-term benefits may require ongoing intervention or lifestyle adherence. The authors also emphasised the need for further research to optimise ECR duration and frequency.[31]

The study conducted by Richard V. Milani, Carl J Lavie, et al highlights how cardiac rehabilitation and exercise training can reduce high-sensitivity C-reactive protein (hs-CRP), study findings showed that a three-month formal phase II rehabilitation programme significantly lowered hs-CRP levels, which suggests that therapeutic lifestyle changes through structured exercise may offer anti-inflammatory benefits beyond pharmacological interventions. While the evidence is promising, further research is needed to confirm the long-term impact of these reductions. The authors also emphasised that larger, multicenter trials with extended follow-up are essential to validate the clinical relevance of hs-CRP modulation through rehabilitation. If future studies continue to demonstrate sustained improvements, cardiac rehabilitation may become a more widely recognised strategy for reducing systemic inflammation in CHD patients.[20]

An evaluation was conducted on how exercise influences inflammatory markers and B-type natriuretic peptide (BNP) in coronary artery disease (CAD). The authors reported that acute exercise temporarily increases markers such as CRP, Mig, and VCAM-1, indicating short-term inflammation. However, after a 4-month structured exercise programme, patients showed reduced inflammatory responses and lower resting BNP levels, suggesting improved cardiac function and reduced stress. While these findings support the anti-inflammatory and cardioprotective effects of regular exercise, the sample size was modest, and long-term outcomes beyond the intervention period remain unclear.[19]

A clinical trial conducted by Claes Held, Harvey D. White, et al has provided insights into the relationship between inflammatory biomarkers and adverse outcomes in patients with stable coronary heart disease (CHD). Study suggest that elevated IL-6 levels were independently associated with increased risks of cardiovascular death, myocardial infarction, heart failure, and even cancer-related mortality. The study highlights the importance of upstream inflammatory pathways in disease progression and supports IL-6 as a potential target for

future therapies. However, further research is needed to explore how modifying IL-6 levels might influence outcomes and whether it can guide personalised treatment strategies.[25]

Limitations

- Studies vary widely in terms of exercise type (e.g., aerobic, resistance, HIIT, MICT), duration (ranging from 3 weeks to 1 year), and intensity.
- Most studies assess outcomes immediately post-intervention, with few extending beyond 6–12 months.
- The sustainability of biomarker improvements (e.g., reductions in hsCRP, IL-6, copetin) over time remains unclear.
- Long-term data are essential to determine whether CR leads to lasting reductions in cardiovascular risk.
- Many studies focus predominantly on male participants, with limited data on women, elderly patients, or those with comorbidities like diabetes or metabolic syndrome. This restricts the generalizability of findings and overlooks potential gender-specific or condition-specific responses to cardiac rehabilitation.
- There is no uniform biomarker panel used across studies; while hsCRP and IL-6 are common, others like BNP, copeptin, VCAM-1, and FGF21 appear sporadically.

Conclusion

Based on the collective evidence from the reviewed studies, exercise based CR emerges as a clinically effective strategy for reducing inflammation in patients with coronary artery disease. Inflammatory biomarkers such as C-reactive protein (CRP), interleukin-6 (IL-6), and copeptin are consistently elevated in CAD and are closely linked to disease progression and adverse cardiovascular outcomes. The findings demonstrate that structured CR programs—particularly those incorporating aerobic and resistance exercise significantly lower these biomarkers, which indicates a reduction in systemic inflammation and improved vascular health.

Furthermore, regular physical activity enhances endothelial function, reduces oxidative stress, and modulates cytokine activity, all of which contribute to the stabilisation of atherosclerotic plaques and improved cardiac performance. Which suggest that personalised rehabilitation protocols may yield optimal results. It has also been shown to improve functional capacity and quality of life, along with its ability to target key biomarkers, which reflects its impact on the biological processes driving coronary pathology. These findings support the integration of exercise-based CR into routine clinical practice, emphasising its value in reducing cardiovascular risk, enhancing recovery, and improving long-term outcomes in patients with coronary artery disease

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