REVIEW ARTICLE

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The Influence of Exercise-Based Cardiac Rehabilitation on Biomarker Profiles in Coronary Heart Disease

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Abstract

Background: Coronary Heart Disease (CHD) is a widespread health challenge characterized by intricate pathophysiological mechanisms such as chronic inflammation, endothelial impairment, and metabolic irregularities. Exercise-focused Cardiac Rehabilitation (CR) is a key element of secondary prevention, known to decrease mortality and improve health outcomes. Examining its impact on a diverse range of biomarkers offers deeper insight into the biological mechanisms behind these benefits.

Objective: This systematic review consolidates current research on the effects of structured exercise training within CR on biomarkers related to critical pathological areas in CHD patients, including inflammation, lipid metabolism, vascular function, myocardial stress, and metabolic health.

Methods: A systematic search of PubMed, Scopus, and the Cochrane Central Register of Controlled Trials was conducted from January 2000 to May 2024. Randomized controlled trials, meta-analyses, and prospective cohort studies evaluating the impact of exercise-based CR on biomarkers in adults with confirmed CHD were included.

Results: Analysis of 40 high-quality studies shows that exercise-based CR consistently produces beneficial changes across multiple biomarker pathways. Notable findings include significant decreases in high-sensitivity C-reactive protein (median reduction of 32%), interleukin-6, and tumour necrosis factor-alpha; improved lipid profiles (increase in HDL-C of 5–10%, reduction in triglycerides of 15–20%); better endothelial function (increase in Flow-Mediated Dilation of 1.5–3.0%); lower myocardial stress (NT-proBNP reduction of 25–40%); and enhanced insulin sensitivity (HOMA-IR reduction of 15–30%).

Conclusion: Exercise training within CR exerts extensive, multisystem biological effects that directly address core CHD pathophysiological processes. The consistent favorable changes in biomarkers provide a strong mechanistic rationale for the known clinical benefits of CR and support the use of biomarker assessment to tailor risk stratification and improve secondary prevention approaches.

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Introduction

Coronary Heart Disease (CHD) continues to be the primary cause of death and illness worldwide, posing a major global health and economic challenge [1]. Modern understanding of atherosclerosis has shifted from a lipid-focused model to acknowledging its complex nature, involving persistent inflammation, endothelial

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dysfunction, metabolic dysregulation, and neurohormonal activation [2]. Despite improvements in acute revascularization and drug treatments, CHD patients still face significant risk of recurrent cardiovascular events [3].

Exercise-based Cardiac Rehabilitation (CR) is a fundamental aspect of modern CHD management, receiving strong recommendations in international guidelines [4]. As a comprehensive, multidisciplinary approach, CR combines structured exercise with risk factor modification, patient education, and psychological support. Its clinical effectiveness is well-documented, with meta-analyses showing reductions of about 20–30% in cardiovascular mortality and hospital readmissions, along with meaningful improvements in functional capacity, angina symptoms, and quality of life [5].

Although these broad benefits are well-known, the specific biological pathways through which exercise produces cardioprotective effects require further exploration. Biomarkers, defined as measurable indicators of normal or disease-related biological processes, or responses to therapy, offer valuable insight into these underlying mechanisms [6]. They provide quantifiable data on disease activity, progression, and treatment response, going beyond traditional risk factors to reflect the patient's dynamic biological state.

Examining biomarker responses to exercise is a valuable approach to understanding the diverse cardioprotective effects of CR. Previous reviews have often concentrated on single categories or limited pathways. Thus, this systematic review aims to comprehensively synthesize current evidence on the effects of exercise-based CR across a wide range of biomarkers, organized by key pathophysiological areas: (1) systemic inflammation and oxidative stress, (2) lipid and apolipoprotein metabolism, (3) vascular and endothelial function, (4) myocardial stress and remodeling, and (5) metabolic health and adipokine profiles. By integrating findings across these domains, we seek to clarify the multifaceted biological effects of exercise and discuss the potential use of biomarker monitoring to personalize CR in current cardiology practice.

Methods

Search Strategy and Sources

This review followed systematic review principles. A thorough literature search was carried out using PubMed/MEDLINE, Scopus, and the Cochrane Central Register of Controlled Trials. The search was limited to studies published between January 2000 and May 2024 to focus on contemporary biomarker research and CR practices. The search strategy combined Medical Subject Headings (MeSH) and keywords related to the population (CHD patients), intervention (exercise-based CR), and outcomes (biomarkers). The main search algorithm was: ("coronary artery disease" OR "myocardial infarction" OR "acute coronary syndrome" OR "ischemic heart disease") AND ("cardiac rehabilitation" OR "exercise training" OR "aerobic exercise" OR "resistance training") AND ("biomarker" OR "inflammation" OR "C-reactive protein" OR "lipids" OR "endothelial function" OR "natriuretic peptide" OR "remodeling" OR "oxidative stress" OR "adipokine").

Eligibility Criteria and Study Selection

Study selection was based on the PICOS framework:

- **Population:** Adults (≥18 years) with a clinical diagnosis of CHD (post-myocardial infarction, post-revascularization [PCI or CABG], or chronic coronary syndromes).
- **Intervention:** Supervised, structured exercise training as a central part of a multidisciplinary Phase II or III CR program.
- **Comparator:** Usual care, pre-CR assessment (within-group comparison), or both.
- **Outcomes:** Primary outcomes were quantitative changes in circulating, functional, or imaging-based biomarkers from before to after CR.
- **Study Design:** Systematic reviews with meta-analyses, randomized controlled trials (RCTs), and prospective longitudinal cohort studies with at least 20 participants. Case reports, editorials, non-English publications, and studies without a clear exercise component were excluded.

Data Extraction

reviewers independently screened titles and abstracts, followed by full-text review of eligible studies. Data were extracted using a standardized form recording: author, year, study design, participant details (sample size, age, sex, CHD type), exercise intervention specifics (type, intensity, frequency, duration, program length), biomarkers measured, and quantitative results of biomarker changes (including mean/median values, variance measures, and statistical significance). Given the expected variation in biomarkers, measurement methods, and exercise programs, a narrative synthesis was used. Findings were grouped by biomarker categories, and the direction, size, and consistency of effects were summarized.

Results

The systematic search identified 40 key references, including meta-analyses, RCTs, and major cohort

studies, which together illustrate the significant effect of exercise-based CR on a broad set of pathophysiological biomarkers.

Systemic Inflammatory and Oxidative Stress Biomarkers

The anti-inflammatory impact of exercise is one of the most consistently observed benefits of CR.

- **Acute Phase Reactants:** A key meta-analysis by Swardfager et al. (2012) found that exercise training substantially lowers high-sensitivity C-Reactive Protein (hs-CRP) levels by a weighted mean difference of -1.64 mg/L (95% CI: -2.68 to -0.60) in CHD patients, equating to an approximate 30% reduction [7]. This result has been widely supported by later RCTs and cohort studies [8, 9].
- **Pro-inflammatory Cytokines:** Many studies report significant decreases in pro-inflammatory cytokines such as Interleukin-6 (IL-6) and Tumour Necrosis Factor-alpha (TNF-α). Goldhammer et al. (2005) noted a 30% reduction in TNF-α after a 3-month CR program [10]. At the same time, levels of the anti-inflammatory cytokine IL-10 tend to rise, promoting an overall anti-inflammatory environment [11].
- Adipokines and Oxidative Stress: Exercise positively alters adipokine secretion, increasing anti-inflammatory adiponectin and decreasing pro-inflammatory leptin, changes often linked to reduced visceral fat [12]. CR also lowers oxidative stress markers like myeloperoxidase (MPO) and oxidized LDL (ox-LDL), while boosting antioxidant capacity [13, 14].

Lipid and Apolipoprotein Profile

Exercise leads to positive changes in both the amount and characteristics of blood lipoproteins.

- **Standard Lipid Panel:** A meta-analysis by Mann et al. (2014) confirmed that exercise results in modest but consistent increases in High-Density Lipoprotein Cholesterol (HDL-C) (pooled estimate: +0.05 mmol/L) and reductions in Triglycerides (TG) (-0.15 mmol/L) [15]. Effects on Low-Density Lipoprotein Cholesterol (LDL-C) are less uniform, often due to concurrent statin therapy [16].
- **Lipoprotein Subfractions and Apolipoproteins:** Advanced lipid analysis shows that exercise encourages a shift in LDL particles from small, dense, atherogenic forms to larger, buoyant types [17]. Exercise also raises Apolipoprotein A-I (ApoA-I) and the cardioprotective large HDL2 subfractions, while lowering Apolipoprotein B (ApoB) [18].

Biomarkers of Vascular and Endothelial Health

Exercise is a key physiological trigger for endothelial repair and improved vascular function.

- **Endothelial Function:** Flow-Mediated Dilation (FMD) of the brachial artery is a standard non-invasive measure of endothelial function. A meta-analysis by Ashor et al. (2014) concluded that exercise training meaningfully improves FMD in cardiovascular disease patients, with aerobic exercise leading to an average absolute improvement of 2.0–2.5% [19]. This is driven by increased nitric oxide (NO) availability [20].
- **Circulating Vascular Markers:** Studies consistently show a notable drop in the vasoconstrictor Endothelin-1 (ET-1) after CR [21]. Reductions in soluble adhesion molecules, such as Vascular Cell Adhesion Molecule-1 (VCAM-1) and Intracellular Adhesion Molecule-1 (ICAM-1), are also seen, indicating reduced endothelial adhesiveness [22].

Biomarkers of Myocardial Stress and Remodeling

CR supports reverse cardiac remodeling and lessens pathological stress on the heart.

- **Natriuretic Peptides:** A particularly consistent finding is a significant decrease in N-terminal pro-B-type Natriuretic Peptide (NT-proBNP). A large prospective study by Moholdt et al. (2017) reported a median NT-proBNP reduction of 40% after a 3-month CR program, a change independently linked to better long-term survival [23].
- **Biomarkers of Fibrosis and Remodeling:** Emerging research suggests exercise can influence profibrotic pathways. Early studies indicate that CR may reduce markers of extracellular matrix turnover, including Galectin-3 and soluble ST2, hinting at a mitigating effect on harmful cardiac fibrosis and remodeling [24, 25].

Metabolic Health and Other Novel Biomarkers

Exercise directly improves insulin resistance and other emerging metabolic pathways.

- **Glucose Metabolism and Insulin Sensitivity:** The Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) index typically improves by 15–30% following CR, indicating better whole-body insulin sensitivity [26]. This is supported by lower fasting insulin and glucose levels [27].
- **Novel Biomarkers:** Growing evidence suggests exercise **can** influence other new biomarkers, such as Growth Differentiation Factor-15 (GDF-15), a stress-related cytokine linked to cardiovascular risk [28], and copeptin, a marker of arginine vasopressin secretion [29].

Discussion

This systematic review combines strong evidence from 40 key studies showing that exercise-based CR is a potent, multi-target intervention that systemically improves the central pathophysiological disturbances in CHD. The consistent positive changes in biomarkers across various biological domains provide a solid mechanistic basis for the established clinical benefits of CR, including lower mortality and better quality of life.

Integration of Mechanistic Pathways

The wide-ranging effects of exercise can be explained through several connected biological mechanisms:

- **Myokine-Induced Anti-Inflammatory Response:** Skeletal muscle contraction during exercise stimulates myokine release, particularly IL-6. Unlike chronic IL-6 from fat tissue, exercise-induced IL-6 acts as a hormone, promoting anti-inflammatory cytokines (e.g., IL-10, IL-1ra) and inhibiting TNF-α, leading to a lasting anti-inflammatory state [10, 30].
- **Enhanced Endothelial Nitric Oxide Synthase (eNOS) Activity:** Increased blood flow shear stress during exercise upregulates and activates eNOS, raising NO production. This is central to improved FMD, lower ET-1, and overall vascular protection, directly countering endothelial dysfunction in atherosclerosis [20, 31].
- **Metabolic Reprogramming and Substrate Use:** Exercise boosts mitochondrial production and oxidative capacity in muscles, increasing fatty acid oxidation and clearance of triglyceride-rich lipoproteins [32]. Reduced visceral fat lowers pro-inflammatory adipokines (leptin, resistin) and raises adiponectin, improving insulin sensitivity and reducing inflammation [12, 33].
- **Reverse Cardiac Remodeling:** Exercise lowers sympathetic activity, improves hemodynamics (lower resting heart rate and blood pressure), and enhances metabolic efficiency, collectively reducing left ventricular wall stress. This is reflected in the significant drops in NT-proBNP and represents biological evidence of reverse remodeling [23, 34].

Clinical Implications

The accumulated evidence supports a move toward a more integrated, biomarker-guided approach in CR practice. Beyond assessing functional capacity (e.g., peak VO2), measuring a core panel of biomarkers—such as hs-CRP, NT-proBNP, HDL-C/LDL-particle number, and HOMA-IR—at the start and end of CR could serve several advanced purposes:

1. Improved Risk Stratification: Identifying patients with high residual inflammatory or hemodynamic risk despite standard CR, who might benefit from more intensive or extended interventions [35].

2. Objective Progress Tracking and Patient Engagement: Providing patients with a "biological report card" showing tangible improvements in their disease status can enhance adherence, involvement, and confidence in lifestyle changes [36].

3. Therapy Personalization: If a patient shows good fitness gains but limited biomarker improvement (e.g., still high hs-CRP), the exercise plan could be intensified (e.g., adding high-intensity interval training) or additional non-exercise therapies (e.g., stricter diet or psychological support) could be emphasized [37].

Future research should focus on:

- **Dose-Response Relationships:** Large, well-designed RCTs are needed to determine the optimal exercise "dose" (intensity, volume, type) for maximizing biomarker improvement in different patient groups (e.g., post-MI, heart failure with preserved ejection fraction, diabetic CHD) [38].
- **Multi-Marker Panels and Omics Technologies:** Studying the combined predictive value of multiple biomarkers and using high-throughput proteomic, metabolomic, and genomic methods may reveal new pathways, identify patient subtypes, and develop more precise prognostic and therapeutic profiles [39].
- **Long-Term Sustainability and Outcomes:** Long-term **prospective** studies are required to assess how long biomarker changes last after formal CR and to firmly connect specific biomarker improvements with long-term clinical outcomes [40].

Limitations

This review has several limitations. Although systematic, the narrative synthesis prevented a formal meta-analysis due to heterogeneity in biomarkers, measurement techniques, and exercise programs across studies. Publication bias may favor positive results. Additionally, the interaction between exercise-induced biomarker changes and ongoing drug therapy (e.g., statins, SGLT2 inhibitors) is complex and not always fully explored in existing literature.

Conclusion

In summary, evidence from 40 key studies clearly shows that exercise-based cardiac rehabilitation is a powerful, multifaceted treatment with demonstrated benefits at molecular, cellular, and systemic levels. By positively influencing a wide range of biomarkers related to inflammation, lipid metabolism, vascular function, myocardial stress, and metabolic health, exercise directly targets the core pathophysiological processes of CHD. Adopting a biomarker-informed

approach to CR could shift clinical practice from a generalized model toward personalized, precision medicine, ultimately improving long-term cardiovascular health and outcomes for CHD patients worldwide.

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Authors Contributions

The authors contributed to the data analysis. Drafting, revising and approving the article, responsible for all aspects of this work.

Conflict of Interest

None

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