

INPLASY PROTOCOL

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None declared.

Effects of exercise on the expression of angiogenesis-precursor biomarkers in cardiovascular diseases: a systematic review

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Review question / Objective: What is the effect of exercise on the expression of angiogenesis-precursor biomarkers in cardiovascular diseases?

Condition being studied: Cardiovascular diseases frequently referred to exercise-based cardiac rehabilitation programs, including acute coronary syndrome, ischemic heart disease, heart attack, coronary artery disease, cardiomyopathy, heart failure, arrhythmias, heart valve disease.

Eligibility criteria: Patients 18 years old or over with a clinical diagnosis of any cardiovascular disease previously defined according to the European Society of Cardiology and international guidelines of each disease and who have participated in a rehabilitation program in which their exercise intervention has been systematic, based on clinical guidelines and lasting at least four weeks.

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 17 May 2022 and was last updated on 17 May 2022 (registration number INPLASY202250112).

INTRODUCTION

Review question / Objective: What is the effect of exercise on the expression of angiogenesis-precursor biomarkers in cardiovascular diseases?

Rationale: The neo-formation of new blood vessels in muscle tissue (both cardiac and

skeletal muscle) could be a key variable explaining the patients symptoms and prognosis and explain why adherence to cardiac rehabilitation varies among patients.

Condition being studied: Cardiovascular diseases frequently referred to exercise-based cardiac rehabilitation programs,

including acute coronary syndrome, ischemic heart disease, heart attack, coronary artery disease, cardiomyopathy, heart failure, arrhythmias, heart valve disease.

METHODS

Search strategy: ((Cardiovascular disease) OR (chronic heart disease) OR (coronary artery disease) OR (acute coronary syndrome) OR (arrhythmias) OR (heart valve disease) OR (ischemic heart disease) OR (heart failure) OR (heart attack) OR (Cardiomyopathy) OR (cardiac trasplant)) AND ((physical training) OR (cardiac rehabilitation) OR (exercied-based) OR (aerobic training) OR (strenght training) OR (interval training) OR (hypertrophy)) AND ((VEGF) OR (FGF-2) OR (MMP-9) OR (ANG-1) OR (ANG-2) OR (HGF) OR (MDV) OR (CEC) OR (CEPC)).

Participant or population: Patients 18 years old or over with a clinical diagnosis of any cardiovascular disease previously defined according to the European Society of Cardiology and international guidelines of each disease.

Intervention: Cardiovascular rehabilitation.

Comparator: No intervention or other physical exercise interventions.

Study designs to be included: We will include randomized clinical trials (RCTs), quasi-randomized clinical trials, and observational studies (retrospective, prospective, cross-sectional, longitudinal, case-control and cohort). Editorials, letters, review articles, systematic reviews, and meta-analyses, in vivo and in vitro studies will be excluded.

Eligibility criteria: Patients 18 years old or over with a clinical diagnosis of any cardiovascular disease previously defined according to the European Society of Cardiology and international guidelines of each disease and who have participated in a rehabilitation program in which their exercise intervention has been systematic,

based on clinical guidelines and lasting at least four weeks.

Information sources: We will conduct a systematic review of the literature to identify research investigating the effect of exercise on the expression of angiogenesis-precursor biomarkers in cardiovascular disease. We will search PubMed/MEDLINE, CINALH, Cochrane Library (CENTRAL), Embase, Web of Science, and SCOPUS.

Main outcome(s): Levels of VEGF, FGF-2, MMP-9, ANG-1, ANG-2.

Additional outcome(s): HGF, Capillarization capacity, and morphological changes: Microvessel density (MVD), circulating endothelial cells (CEC), bone-marrow-derived circulating endothelial cell progenitors (CEPC), mitochondrial density, number of muscular fibers, type of muscular fiber, cross-sectional area.

Data management: Studies will be selected for inclusion using the predefined and explicit eligibility criteria. The search results' total articles will be screened independently by two reviewers (ICA-GL) to identify all citations that meet the inclusion criteria. Also, the full manuscripts of the selected citations will be retrieved and assessed by two reviewers (ICA-GL) against the inclusion criteria. Any disagreements about the inclusion of any study will be resolved by consensus or, if necessary, by arbitration by a third reviewer (RTC). Study characteristics, baseline patients' characteristics, duration of intervention, type/setting of exercise, type of biomarkers, and outcomes will be extracted from the studies selected for inclusion by two reviewers (ICA-GL) using pre-designed and piloted data extraction form to avoid any errors. Any disagreements between reviewers will be resolved by consensus or, if necessary, by arbitration by a third reviewer (RTC). Authors may be contacted to request potential missing data on a case-by-case basis, considering the importance and relevance of data that is missing.

Quality assessment / Risk of bias analysis:

The risk of bias in the included studies will be assessed with the Critical Appraisal tools of JBI, following recommendations of JBI Manuals for Evidence Synthesis. The studies will be graded independently by 2 reviewers (ICA-GL) to minimize bias. Scores will be compared, and discrepancies will be sorted by a third reviewer (RTC).

Strategy of data synthesis:

We will provide a narrative synthesis of findings from the included studies. We will report summaries of the association between risk factors and outcomes for each study regarding mean differences or standardized mean differences. If a meta-analysis is appropriate, we will estimate pooled measures of association using a random-effect meta-analysis and calculate 95% confidence intervals for each outcome. A forest plot will be created to display results to assess the direction and magnitude of the effects, and overlap between confidence intervals could be analyzed. Statistical heterogeneity will be assessed using Cochran's Q value and the I² statistics from the standard X² test. If I² >50%, this will be considered to reflect significant statistical heterogeneity. When I² >50% the random-effects model using the inverse variance heterogeneity method will be used. A sensitivity analysis excluding one study at a time will also be undertaken to identify the origin of heterogeneity. Funnel plots will be constructed.

Subgroup analysis: By specific disease and type/setting of exercise training.

Sensitivity analysis: We will perform sensitivity analysis based on sample size, heterogeneity, methodological quality, and statistical model. We will exclude studies with low quality and ensure the stability of analysis results.

Language: No restriction.

Country(ies) involved: Spain and Chile.

Keywords: angiogenesis-precursor biomarkers; exercise; cardiac rehabilitation; cardiovascular disease.

Dissemination plans: Presentation on national or international congress of cardiology and subsequent publication in high-impact journals.

Contributions of each author:

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