

Abstract

Cardiovascular diseases remain the leading cause of death worldwide, with acute coronary syndrome (ACS) representing one of the most serious clinical manifestations of atherosclerotic cardiovascular disease. Contemporary management of ACS extends beyond acute revascularization and guideline-directed pharmacotherapy to include comprehensive secondary prevention, in which phase II cardiac rehabilitation plays a pivotal role.

The effectiveness of post-ACS management is traditionally evaluated using established cardiovascular risk factors. However, increasing attention has recently been directed toward novel biomarkers that may provide a more comprehensive understanding of the biological mechanisms underlying atherosclerosis progression and recovery following myocardial injury. Among these, proteomic profiling has emerged as a promising approach for characterizing inflammatory processes, identifying molecular pathways involved in atherosclerosis, and assessing the biological response to therapeutic interventions.

Advances in high-throughput proteomic technologies now enable the simultaneous quantification of thousands of proteins, facilitating the discovery of novel biomarkers and providing deeper insight into the complex pathophysiological mechanisms associated with ACS and its treatment.

1. Objectives

This study aimed to evaluate the effects of a complete phase II comprehensive cardiac rehabilitation (CR) programme combined with intensive health education on conventional cardiovascular risk factors, serum proteomic profile, and health-related quality of life in patients following acute coronary syndrome (ACS).

2. Methods

This prospective study enrolled 78 patients hospitalized with acute coronary syndrome (ACS) at the Department of Cardiology, Hypertension and Internal Medicine, Medical University of Warsaw, Bródnowski Hospital, between 2019 and 2023.

The study comprised two assessment phases. During phase 1, conducted throughout the index hospitalization, demographic and clinical data were collected using a dedicated questionnaire. Conventional cardiovascular risk factors were evaluated by

measuring fasting lipid profile, fasting plasma glucose, resting blood pressure, and body mass index (BMI). Functional capacity was assessed using a symptom-limited treadmill exercise test according to the Bruce protocol. Health-related quality of life was evaluated using the World Health Organization Quality of Life-BREF (WHOQOL-BREF) questionnaire.

Following discharge, all patients were invited to participate in a comprehensive phase II cardiac rehabilitation (CR) programme. Participation was voluntary and based exclusively on the patient's decision. Patients who completed the full rehabilitation programme constituted the rehabilitation group ($n = 63$), whereas those who declined participation formed the non-rehabilitation group ($n = 15$).

Phase 2 was performed after completion of phase II CR in the rehabilitation group and approximately 8 weeks after the index ACS event during a scheduled follow-up visit in the non-rehabilitation group. The clinical assessment performed at follow-up included repeat measurements of fasting lipid profile, fasting plasma glucose, resting blood pressure, body weight, treadmill exercise testing according to the Bruce protocol, and reassessment of health-related quality of life using the WHOQOL-BREF questionnaire.

To investigate non-classical cardiovascular risk factors, a proteomic substudy was performed. Peripheral venous blood samples (10 mL) were collected during both study phases from participants included in the proteomic analysis.

The proteomic cohort comprised 20 men with ACS and 10 men without cardiovascular disease who served as healthy controls. The ACS cohort was subsequently divided into patients who completed phase II CR ($n = 15$) and those who declined rehabilitation ($n = 5$).

Statistical analyses were performed using STATISTICA version 13 (StatSoft, Poland) and GraphPad Prism version 7 (GraphPad Software, USA). Data distribution was assessed using the Shapiro–Wilk test. Depending on data distribution, comparisons were performed using Student's t -test, the Mann–Whitney U test, the Wilcoxon signed-rank test, or the χ^2 test, as appropriate. A two-sided p value <0.05 was considered statistically significant.

The study protocol was approved by the Bioethics Committee of the Medical University of Warsaw (approval No. KB/174/2019).

3. Results

Exercise capacity improved significantly between baseline (phase 1) and follow-up (phase 2) in both study groups. In patients who completed phase II cardiac rehabilitation, median exercise capacity increased from 7.0 [7.0 – 7.2] to 10.2 [7.0 – 10.2] metabolic equivalents (METs) ($p < 0.001$). In the non-rehabilitation group, METs increased from 7.0 [5.7 – 8.1] to 7.1 [6.7–10.0] ($p < 0.001$).

A significant reduction in BMI was observed only in the rehabilitation group (28.42 ± 4.06 vs. 28.13 ± 3.90 kg/m²; $p < 0.001$), whereas no significant change was detected among patients who did not participate in cardiac rehabilitation. Resting blood pressure, HDL cholesterol, and fasting plasma glucose remained unchanged in both groups throughout the study period. Triglyceride concentrations decreased in both groups; however, statistical significance was reached only in the non-rehabilitation group (147 ± 72 vs. 108 ± 60 mg/dL; $p = 0.01$). LDL cholesterol decreased significantly in both groups, from 118 [77–148] to 66 [53–83] mg/dL ($p < 0.001$) in the rehabilitation group and from 120 ± 27 to 79 ± 24 mg/dL ($p < 0.001$) in the non-rehabilitation group. No significant between-group differences were observed for any of the analysed clinical variables at either baseline or follow-up.

Baseline assessment of health-related quality of life demonstrated that patients who subsequently participated in cardiac rehabilitation reported poorer quality of life than those who declined rehabilitation. Significant between-group differences were observed for overall quality of life (Question 1: 3 [3 – 4] vs. 4 [4 – 4]; $p = 0.02$), the physical domain (13.40 ± 2.34 vs. 15.60 ± 2.82 ; $p = 0.01$), the psychological domain (15.18 ± 2.53 vs. 17.53 ± 2.00 ; $p < 0.001$), and the environmental domain (15.11 ± 2.43 vs. 16.33 ± 1.95 ; $p = 0.05$).

At follow-up, these baseline differences were no longer evident. Although no significant between-group differences were found after 6–8 weeks, participants who completed phase II cardiac rehabilitation demonstrated significant within-group improvements in overall quality of life (3 [3 – 4] vs. 4 [4 – 4]; $p < 0.001$), satisfaction with health (3 [2 – 4] vs. 3 [3 – 4]; $p < 0.001$), the psychological domain (15.00 ± 2.51 vs. 15.56 ± 2.30 ; $p = 0.03$), and the environmental domain (15.05 ± 2.47 vs. 15.60 ± 2.37 ; $p = 0.04$). In contrast, patients who declined cardiac rehabilitation showed only non-significant improvements in satisfaction with health and the social domain, whereas numerical deterioration was observed in the remaining WHOQOL-BREF domains compared with baseline.

Proteomic profiling identified a total of 4,702 proteins. Compared with healthy controls, patients with acute coronary syndrome (ACS) exhibited significant differences in the abundance of 19 proteins ($\log_2\text{FC} \neq 0$; $p < 0.05$). Twelve proteins were significantly more abundant, including proteins involved in complement activation (C2, C3, C5, C6, C8A, and C9), haptoglobin, apolipoprotein(a), alpha-1-antitrypsin, alpha-1-antichymotrypsin, plasma protease C1 inhibitor, and transthyretin. Conversely, seven proteins showed significantly lower abundance, namely alpha-2-HS-glycoprotein (fetuin-A), apolipoprotein A-I, apolipoprotein A-IV, apolipoprotein C-III, apolipoprotein E, complement C1q subcomponent subunit C, and calcineurin subunit B type 1 ($\log_2\text{FC} < 0$; $p < 0.05$).

Following completion of phase II cardiac rehabilitation, significant alterations in the abundance of 33 proteins were identified in the rehabilitation group. Eight proteins were significantly upregulated ($\log_2\text{FC} > 0$; $p < 0.05$), including beta-alanine-activating enzyme, apolipoprotein A-I, apolipoprotein C-III, complement C1q subcomponent subunit C, ribonuclease 3, immunoglobulin lambda constant region 2, integrin alpha-9, and zinc finger RNA-binding protein. In contrast, 25 proteins were significantly downregulated ($\log_2\text{FC} < 0$; $p < 0.05$), including afamin, serum amyloid P-component, apolipoprotein B-100, apolipoprotein M, complement C1s subcomponent, complement component C6, complement component C8 alpha chain, complement component C9, centrosome-associated protein CEP250, complement factor H, complement factor I, clusterin, ceruloplasmin, fibronectin, vitamin D-binding protein, haptoglobin, haptoglobin-related protein, immunoglobulin heavy variable 3-23, leucine-rich alpha-2-glycoprotein, alpha-1-acid glycoproteins 1 and 2, serum paraoxonase/arylesterase 1 OS, vitamin K-dependent protein S, alpha-1-antichymotrypsin, and UDP-glucuronosyltransferase 1-1. In the non-rehabilitation group, significant changes were observed in eight proteins. Five proteins were significantly upregulated ($\log_2\text{FC} > 0$; $p < 0.05$), namely complement C1q subcomponent subunit B, immunoglobulin lambda constant region 7, Rho guanine nucleotide exchange factor 38, immunoglobulin heavy constant gamma 4, and gelsolin, whereas three proteins - immunoglobulin heavy constant alpha, vitamin K-dependent protein S, and apolipoprotein A-I - were significantly downregulated ($\log_2\text{FC} < 0$; $p < 0.05$).

4. Conclusions

- 1) Conventional cardiovascular risk factors associated with atherosclerosis did not change significantly in patients following acute coronary syndrome (ACS) who

underwent comprehensive phase II cardiac rehabilitation (CR) combined with intensive health education during the 8-week follow-up period, compared with patients who did not participate in phase II CR.

- 2) Comprehensive phase II cardiac rehabilitation was associated with improved health-related quality of life, particularly in the physical, psychological, and environmental domains assessed using the WHOQOL-BREF questionnaire.
- 3) Acute coronary syndrome was associated with significant alterations in the serum proteomic profile, predominantly involving proteins related to the inflammatory response, the complement system, and lipid metabolism, reflecting the activation of pathophysiological processes accompanying myocardial injury.
- 4) Participation in phase II cardiac rehabilitation was associated with changes in the abundance of selected proteins, which may reflect modulation of inflammatory and metabolic processes during the recovery period following acute coronary syndrome.