Original Article

The improvement in aerobic capacity, disease activity, and function in patients with rheumatoid arthritis following cardiac rehabilitation program: A single-center, controlled study

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ABSTRACT

Objectives: This study aims to evaluate the effect of cardiac rehabilitation (CR) on disease activity, functional status, fitness, and modified cardiovascular disease (CVD) risk factors in patients with rheumatoid arthritis (RA) with a moderate disease activity.

Patients and methods: This single-center, controlled study included a total of 60 female RA patients (mean age 57.5 years; range, 50 to 64 years) with moderate disease activity according to the Disease Activity Score-28 (DAS28) between January 2014 and June 2015. The patients were divided into two equal groups as those receiving CR program (n=30) and those receiving home exercise program (HEP; n=30). The patients were evaluated at baseline, at Weeks 10 and 24 using exercise tolerance test (i.e., The Metabolic Equivalent of Task [MET] and maximal oxygen uptake [VO₂ max]), Six-Minute Walk Test (6MWT), DAS28, Health Assessment Questionnaire (HAQ), modified Systematic Coronary Risk Evaluation (mSCORE), Short Form Health Survey-36 (SF-36), and Beck Depression Inventory (BDI).

Results: There was a significant improvement in the VO₂ max (p<0.001), MET (p<0.001), DAS28 (p<0.001), HAQ (p<0.001), BDI (p=0.005), SF-36 physical function (p=0.039), pain (p<0.001) and vitality subscale scores (p=0.008), and 6MWT (p<0.001), after the initial and repetitive exercise programs in the CR group compared to the HEP group. At the end of Week 24, full compliance with HEP was higher in the patients with CR group, compared to the HEP group (p<0.001). There was no significant effect of supervised exercise program on the mSCORE, although systolic blood pressure (p=0.033) and resting heart rate (p=0.049) were significantly improved in the CR group versus HEP group.

Conclusion: Based on our study results, supervised exercise program cannot reduce CVD risk as assessed by the mSCORE, although it improves physical fitness, disease activity, and functional outcomes which may reduce traditional CVD risk factors in patients with RA.

Keywords: Cardiac rehabilitation, cardiovascular risk, home exercise, rheumatoid arthritis.

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by symmetric peripheral synovial joint involvement. It can also cause systemic involvement via tissue and organ damage.[1] Extra-articular involvement may be seen in about 40% of patients.[2] Extra-articular involvement is related to increased morbidity and early mortality.[2] Cardiovascular (CV) involvement is the most common cause of death in RA. In the literature, CVD risk has been shown to increase by 50% in RA patients, compared to general population.[3]

Rheumatoid arthritis and CVD share similar inflammatory mechanisms.[4] Longer disease duration, higher disease activity, and elevated acute phase reactants are associated with the development of atherosclerosis.[5] In addition to an increased atherosclerosis risk, a higher level of physical inactivity is common in patients with RA, compared to general population. Physical inactivity has been also shown to be associated with decreased life expectancy.[6] It is also thought to be an independent risk factor for heart disease such as diabetes mellitus (DM) or hypertension (HT).[7]

Recent guidelines recommend evaluating and treating the CVD risk in patients with RA. The European League Against Rheumatism (EULAR) suggests using modified Systematic Coronary Risk Evaluation (mSCORE) risk assessment profile for calculation and management of CVD risk in RA patients.[8] Controlling inflammation and disease activity are the most important factors for risk reduction. Furthermore, assessment of general CVD risk factors such as hyperlipidemia (HL), obesity, and smoking is also suggested.[8]

Cardiac rehabilitation (CR) is usually described as medically supervised program which helps to improve the health and well-being of individuals with heart diseases.[9] The cornerstone activity of CR programs is regular and well-planned exercises. These programs include exercise training, education on heart-healthy living, and counseling to reduce stress, and help return to an active life. Cardiorespiratory aerobic exercises improve some of the most important RA patient outcomes including function, quality of life, compliance, and pain. Moreover, it appears that aerobic exercise decreases radiological damage and pain and adverse events, indicating that exercises were safe in stable RA.[9] However, there is limited information about the cardiac risk management in patients with RA. Previous studies about exercises in RA have mostly focused on the functional status rather than the cardiac risk management. These studies have emphasized that exercise may improve the Disease Activity Score of 28 joints (DAS28) and Health Assessment Questionnaire (HAQ) scores which are the indicators of disease activity and functional status.[9,10]

In the present study, we aimed to compare the effect of CR program and home exercise program (HEP) on disease activity, functional status, fitness parameters, and CVD risk factors in patients with established RA with a moderate disease activity.

PATIENTS AND METHODS

This cross-sectional, observational study, single-center, controlled study included a total of 60 female RA patients (mean age 57.5 years; range, 50 to 64 years) who met the American College of Rheumatology (ACR)/EULAR 2010 classification criteria[8] with moderate disease activity according to the DAS28 between January 2014 and June 2015. Inclusion criteria were as follows: female sex, age between 45 to 75 years; having a DAS28 score of 3.2 to 5.1. Patients who had a DAS28 score of <3.2 or >5.1, contraindication for exercise stress test, coronary artery disease, congestive heart failure,
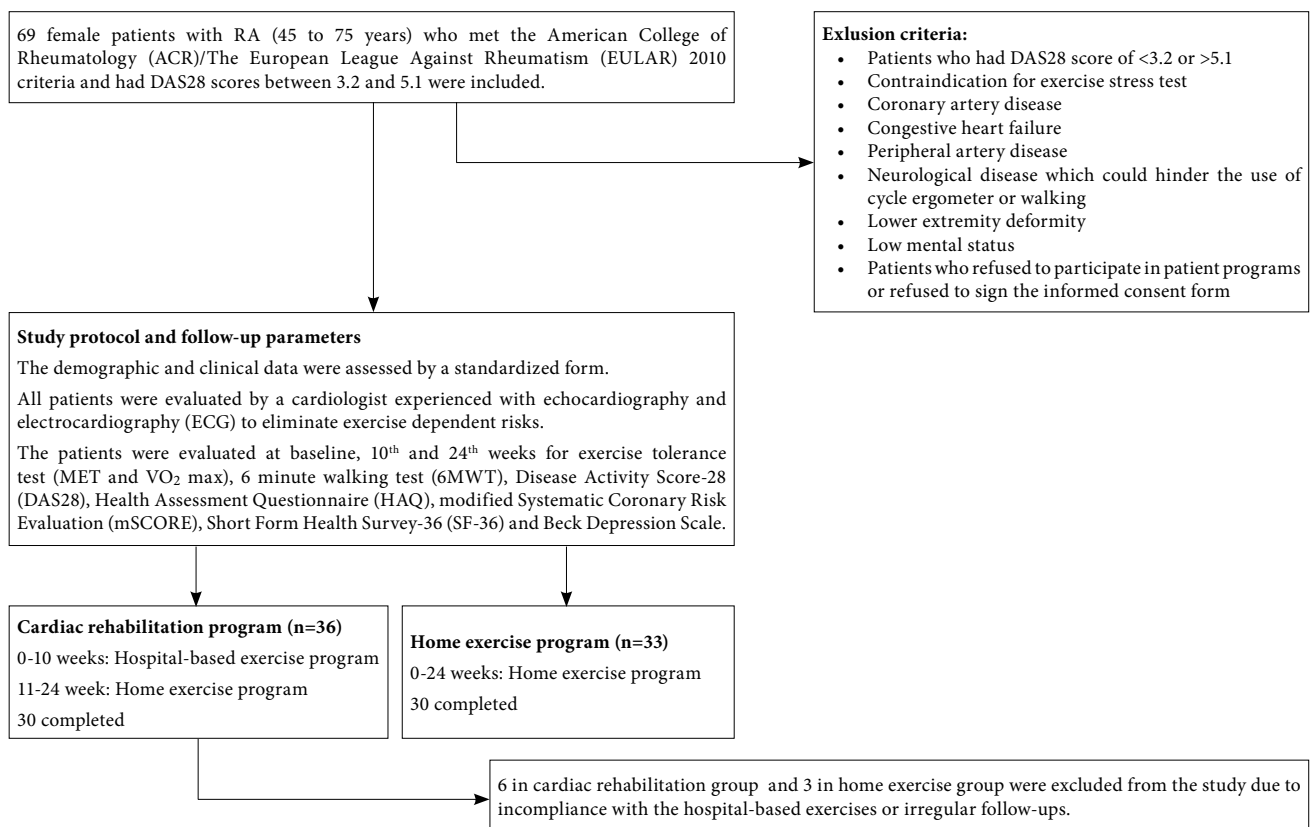
peripheral artery disease, or neurological disease which could hinder the use of cycle ergometer or walking, and those with lower extremity deformity, and low mental status were excluded from the study.

Initially, 66 patients who were volunteer to participate in the study were numerated. The patients were randomly divided into two groups as CR and HEP by a web-based shareware. There were 36 patients in CR group and 33 patients in HEP group. Six patients in the CR group and three patients in the HEP were excluded from the study due to incompliance with the hospital-based exercises or irregular follow-ups. Finally, the study was completed with 30 patients in each group. The patients with RA were managed by followed-up under tight control in a single rheumatology center and all treatment decisions were made based on the target-to-treat strategy during exercise program. A written informed consent was obtained from each patient. The study protocol was approved by the Marmara University, Faculty of Medicine, Medical Ethics Committee (ID: 09.2013.0412). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Demographic data and disease activity were assessed by the first clinician using a standardized form. Age, height, weight, body mass index (BMI), anti-citrullinated protein antibodies (ACPA), rheumatoid factor (RF), lipid profiles, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) values, left ventricular ejection fraction (LVEF), occupation, prevalence of HT, DM, HL, chronic kidney disease (CKD), thyroid disorders, respiratory system diseases, smoking, RA duration, medical drug regimens, and presence of extra-articular involvement were recorded. The Short Form Health Survey-36 (SF-36), DAS28, HAQ, and Beck Depression Inventory (BDI) forms were filled out by each patient. The DAS28 score and mSCORE risk profile were calculated. All patients were evaluated by a cardiologist experienced with echocardiography and electrocardiography (ECG) to eliminate exercise-dependent risks and referred to the second clinician who performed the exercise testing and Six-Minute Walk Test (6MWT) (Figure 1). All participants in the study underwent a standardized education including CVD risk factors in RA, importance of physical activity, healthy diet, and health consequences of smoking.

Follow-up parameters

The SF-36 is a generic measure for assessing the quality of life which has eight subscales such as physical functioning, physical role limitations, pain,

69 female patients with RA (45 to 75 years) who met the American College of Rheumatology (ACR)/The European League Against Rheumatism (EULAR) 2010 criteria and had DAS28 scores between 3.2 and 5.1 were included.

Exlusion criteria:
- Patients who had DAS28 score of <3.2 or >5.1
- Contraindication for exercise stress test
- Coronary artery disease
- Congestive heart failure
- Peripheral artery disease
- Neurological disease which could hinder the use of cycle ergometer or walking
- Lower extremity deformity
- Low mental status
- Patients who refused to participate in patient programs or refused to sign the informed consent form

Study protocol and follow-up parameters

The demographic and clinical data were assessed by a standardized form.

All patients were evaluated by a cardiologist experienced with echocardiography and electrocardiography (ECG) to eliminate exercise dependent risks.

The patients were evaluated at baseline, 10th and 24th weeks for exercise tolerance test (MET and VO₂ max), 6 minute walking test (6MWT), Disease Activity Score-28 (DAS28), Health Assessment Questionnaire (HAQ), modified Systematic Coronary Risk Evaluation (mSCORE), Short Form Health Survey-36 (SF-36) and Beck Depression Scale.

Cardiac rehabilitation program (n=36)

0-10 weeks: Hospital-based exercise program

11-24 week: Home exercise program

30 completed

Home exercise program (n=33)

0-24 weeks: Home exercise program

30 completed

6 in cardiac rehabilitation group and 3 in home exercise group were excluded from the study due to incompliance with the hospital-based exercises or irregular follow-ups.

Figure 1. Study flowchart.

general health perceptions, vitality (energy), social function, emotional status, and mental health. The Turkish validity and reliability studies were done by Koçyiğit et al.[11]

The HAQ was developed to assess functional disability in patients with RA. In eight subscales constituting of dressing and personal care, stand up, getting out of bed, eating and drinking movements, walking and climbing stairs, washing-toilet, reaching high and low, hand grip and daily activities, it includes questions related to the 20 daily living activities. Total scores between 0-1 indicate mild; 1.1-2 moderate, and 2.1-3 severe functional loss.[12] Validity and reliability studies in Turkish were conducted by Küçükdeveci et al.[13]

The BDI is a scale which consists of 21 questions, where behaviors related with depressive affect are questioned. The validity and reliability studies were carried out by Hisli[14]

The 6MWT measures the submaximal exercise capacity indirectly which is commonly used in cardiopulmonary rehabilitation. It is reported to be correlated with aerobic capacity (VO₂ max).

Before starting the test, patients were seated for 15 min to rest. Although normal values can be changed due to age, sex, and BMI, values between 400 to 700 meters were accepted as normal range. Absolute contraindications include unstable angina and myocardial infarction within the last one month, while resting blood pressure (BP) over 180 mmHg and resting heart rate (HR) above 120 beats per minute are considered relative contraindications for the test. Minimal significant change for improvement criterion in the 6MWT was found to be 54 meters according to a previous study.[15]

The mSCORE risk assessment profile is based on the EULAR guidelines.[8] Ten-year risk of fatal CVD was calculated using variables such as age, sex, smoking, systolic blood pressure (SBP), and total cholesterol (TC)/high-density lipoprotein (HDL) ratio, according to the SCORE model. Then, a 1.5-multiplication factor was used, when the patient with RA meets two of three criteria which are disease duration of more than 10 years, RF or ACPA positivity, presence of certain extra-articular manifestations.[8]

The DAS28 is a measure of disease activity in RA. It considers 28 tender and swollen joint counts,

general health (GH; patient assessment of disease activity using a 100 mm visual analog scale [VAS] with 0= best, 100= worst), plus levels of an acute phase reactant (either ESR [mm/h] or CRP [mg/L]). A DAS28 of higher than 5.1 indicates active disease; less than 3.2 low disease activity; and less than 2.6 remission.[16]

The exercise tolerance test was applied in CR unit two days after the first evaluation. Contraindications for exercise test were assessed by a cardiologist. Cycle ergometer (Ergoline Ergoselect 2 model 600 and Opticare software program) was used to assess the exercise capacity.[17] All patients were instructed to wear comfortable clothes, stopped eating/drinking for three hours before their arrival, and did not smoke before the test. Maximum heart rate (MHR) and target heart rate (THR) range were calculated according to age and sex, and Karvonen formula [(MHR- resting HR) × % intensity + resting HR], respectively.[18] During the test, the patient started cycling with 30 watts pedal load and 15 watts increment was applied every two min with a constant pedaling speed of 55 to 65 per min. If THR was reached or the patient wanted to stop due to fatigue, the test was stopped. Reached maximum pedal load in watts, maximal oxygen consumption in min per kg or the metabolic equivalent of task (MET) (mL/kg/min) and maximal energy consumption (kcal/min) were recorded. The data were used to develop individualized rehabilitation program of patients in CR group and also used as a follow-up criterion of fitness parameters for both groups.

Rehabilitation approach in the CR group: Initially the ratio of maximum load to patient body weight (watt/kg) was calculated. The ratio was used as an indicator of physical fitness. The values lower than 1.4 watt/kg indicated an untrained person or patients with moderate-to-high risk for cardiac complications during physical stress according to the recommendations of the American Heart Association.[19] If the ratio was lower than 1 watt/kg, the patients started the program with low-intensity intermittent training for providing the compliance of the patient with the program. When the ratio was ≥1, exercise program was continued with constant HR (endurance training) method. Individual exercise programs were revised weekly by assessments including the Borg scale, MHR at maximal load, ECG, and BP monitorization during the exercises.

Each training session included reduced load warming and cooling periods for five min in the beginning and the end. In the intermittent training program, the patients performed one-min low intensity and maximum load consecutively for 20 min under supervision of the second clinician. Using the constant HR method, the maximal load at THR was recorded with the exercise testing. In the program, the patients exercised without exceeding THR. The THR was kept in constant with changing the load automatically by cycle ergometer.

Each exercise session was ended with stretching and strengthening exercises. Biceps, triceps, deltoid, quadriceps, hamstrings, abductor muscle groups were trained in the muscle strengthening program. Strengthening exercises were planned with calculation of one repetition maximum (RM) method. The maximum load which can be hold by three different large muscle groups of lower and upper extremities was determined. Each muscle was strengthened with 3×10 repetitive isotonic contractions with up to 75% resistance of one RM.

Hospital-based exercise program was performed three days per week between Weeks 1 and 10. After Week 10, HEP was performed in the patients and they were assessed at Week 24. During the HEP, the patients were called weekly via telephone by the second clinician to increase compliance with the exercise program. At Week 24, the patients were questioned with a simple questionnaire about their compliance to HEP. The patients who did not perform the aerobic exercise program were accepted as incompliant patients.

HEP group: According to the exercise capacity, the patients were recommended to perform a HEP. The program included 20 to 45 min brisk walking for three times a week and proceeding with stretching and strengthening exercises of lower and upper extremity muscles. The training program was planned for each patient individually by the second clinician. The patients were called weekly via telephone and were encouraged to comply with the HEP. The patients were evaluated at Weeks 10 and 24. Their compliance with HEP was also questioned at Week 24.

Statistical analysis

Statistical analysis was performed using the IBM SPSS for Windows version 19.0 software (IBM Corp., Armonk, NY, USA) and R free software v.3.5.1 with nparLD package (Institute for Statistics and Mathematics, Vienna, Austria). Power analysis was performed before the study. Based on a previous study, the effect size was 17% for VO$_2$ max parameter.[20] Minimum 11 subjects in each group would be necessary to detect significant difference at an alpha level of

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5% (=0.05) with an 80% probability (=0.2). Normal distribution of data was analyzed using the Kolmogorov-Smirnov test. Descriptive statistics were expressed in mean ± standard deviation (SD) or number and frequency. Categorical values were analyzed using the chi-square test. Repeated measures analysis of variance (ANOVA) and Brunner-Langer test (non-parametric repeated measures ANOVA) and analysis of covariance (ANCOVA) with one between-subjects factor (group: CR vs. HEP) and one within-subjects factor (time: baseline vs. Week 10 vs. Week 24) were used to investigate the changes in disease activity, functional status, fitness, and CVD risk factors between the groups at the three different time points. The Tukey honestly significant difference (HSD) method was used to detect where the differences in the evaluation points occurred (baseline vs. Week 10 vs. Week 24). A *p* value of <0.05 was considered statistically significant with 95% confidence interval (CI).

RESULTS

The comparison of baseline characteristics between the groups is shown in Table 1. Age, height, weight, body mass index, ACPA and RF levels, LVEF, occupation, prevalence of HT, DM, HL, CKD, thyroid disorders, respiratory system diseases, smoking status, RA duration, medical drug regimens and presence of extra-articular involvement were similar between the groups.

Fitness parameters: While the CR and HEP groups had similar MET values at baseline, MET values of CR group at Weeks 10 and 24 were significantly higher than HEP group (p<0.001). A statistically significant difference was also detected between the values of baseline and Week 10 and between baseline and Week 24 in favor of the CR group according to the Tukey HSD method (F Week 10 and baseline: p<0.001; Week 24 and baseline: p=0.001) (Figure 2). Statistical analysis of the VO_2 max (p<0.001), maximum energy consumption (p=0.001), maximum load (p<0.001), and 6MWT (p<0.001) parameters had a significantly similar pattern of results with MET. Although two groups had similar values at baseline, values of CR group at Weeks 10 and 24 were significantly better than HEP group (Table 2). In ANCOVA test, all fitness parameters had significant differences between two groups at different time points (baseline vs. Weeks 10 and 24) (for all p<0.05) (Table 5).

Functional measurements: The parameters about the functional scores and DAS28 are demonstrated

in Table 3. The SF-36 physical function and pain subscale scores of CR group were significantly higher than HEP group [(p=0.039; p<0.001, respectively)] although no statistically significant difference in the SF-36 physical function subscale was observed between the values of baseline vs. Week 24 in favor of CR group according to the Tukey HSD method. In SF-36 vitality subscale, CR group had lower scores at baseline which increased at Week 10 (Tukey HSD p=0.001) in CR group, and reached a similar level for both of the groups at Week 24 (Tukey HSD p=0.021) (ANOVA p=0.008). The SF-36 general health perception, physical role subscales, social function, emotional status, and mental status subscales were similar between two groups at the three different time points. The HAQ scores of CR group at Weeks 10 (Tukey HSD p<0.001) and 24 (Tukey HSD p<0.001) were found to be lower than the scores of HEP group (ANOVA p<0.001). A significant difference regarding the BDI was observed in CR group. At baseline, both groups had similar scores, although the scores of CR group were found to be statistically lower than HEP group (p=0.025).
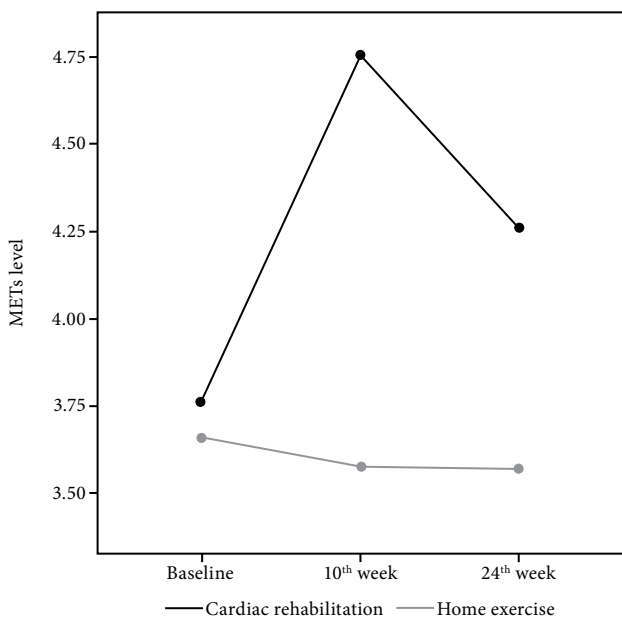
The ANCOVA test revealed that the SF-36 vitality and emotional status subscales and HAQ scores were significantly different between two groups at different time points (baseline vs. Weeks 10 and 24), although the SF-36 physical role, pain, physical function, general health perception and social function subscale and BDI scores were significantly different at only Week 10 (for all p<0.05) (Table 5).

Disease activity measurements: A statistically significant difference was found between two groups in terms of DAS28 scores (p<0.001). The baseline scores were similar for both groups; however, DAS28 scores significantly decreased in CR group and were significantly lower than HEP group (p<0.001). The number of patients who showed significantly ≥0.6 improvement in DAS28 scores was 20/30 (65%) in CR group and 4/30 (15%) in HEP group (p=0.04). In repeated measurements, global assessment scores of CR group were significantly lower than HEP group (p<0.001). There were no statistically significant differences in baseline CRP and ESR values between the groups. The number of swollen joints was similar between the groups at different time points, although a significant difference was observed regarding the tender joint count between the groups in repeated measurements (p<0.001). At baseline, scores were similar for both groups, while the tender joint count significantly decreased in CR group after repeated measurements (p<0.001).

TABLE 1
Demographic and clinical characteristics of patients

	CR group (n=30)					HEP group (n=30)					p
	n	%	Mean±SD	Median	Min-Max	n	%	Mean±SD	Median	Min-Max	
Age (year)			57.9±6.1		50-64			57.4±5.1		51-63	0.756
Height (cm)			158.8±4.3		151-165			162.3±6.7		153-169	0.161
Weight (kg)			78.9±13.7		61-94			81.1±14.1		59-38	0.625
Body mass index (kg/m^2)			31.3±5.3		23-39			31.2±5.5		21-41	0.951
LVEF (%)			65.2±3.9		60-71			66.0±5.8		60-72	0.603
Occupation											0.559
House wife	25	84				28	94				
Retired	2	6				2	6				
Worker	3	10				0	0				
Hypertension	14	45				21	70				0.259
Diabetes mellitus	10	35				10	35				1
Hyperlipidemia	6	20				6	20				1
Chronic kidney disease	0	0				1	3				0.311
Thyroid disorders	3	10				1	3				0.548
Respiratory disorders	3	10				0	0				0.147
Smoking	105	50				12	40				0.525
Rheumatoid arthritis duration (year)			13.9±4.4		4-18			13.5±3.3		5-17	0.612
Extra-articular involvement	8	25				3	10				0.212
Rheumatoid factor (IU/mL)				25	20-103.7				21	20-93.5	0.328
ACPA (IU/mL)				3.6	1.5-126.5				3.1	1.3-79.5	0.239
Medical drug regimens											
Methotrexate											
Corticosteroid											
Hydroxychloroquine											
Leflunomide											
Biologics											
Methotrexate + corticosteroid											
DMARD combinations											
DMARD combinations + corticosteroid											

CR: Cardiac rehabilitation; HEP: Home exercise program; SD: Standard deviation; Min: Minimum; Max: Maximum; LVEF: Left ventricular ejection fraction; ACPA: Anti-citrullinated protein antibody; DMARD: Disease-modifying antirheumatic drug.

Figure 2. Changes in MET values from baseline to Weeks 10 and 24 for cardiac rehabilitation versus home exercise groups.
MET: Metabolic equivalent of task.

According to the ANCOVA test, DAS28 and global assessment scores and tender joint count were significantly different between two groups at different time points (baseline vs. Weeks 10 and 24), although swollen joint count was significantly different at only Week 10 (for all p<0.05) (Table 5).

Cardiovascular risk analysis: All patients included in the study had a mSCORE risk profile with a mean value of 3. The mean values exceeded 3 in 50/60 patients. There was no significant difference regarding the mSCORE risk profile analysis between the groups at different time points. A significant decrease was observed in the SBP in CR group (p=0.033). However, TC/HDL ratio was similar between groups. The resting HR of both groups were similar before the study, although in CR group, there was a statistically significant decrease during follow-up (p=0.049) (Table 4).

The ANCOVA test revealed that mSCORE risk profile, SBP, and resting HR were significantly different at only Week 10 between two groups (for all p<0.05) (Table 5).

HEP compliance: At the end of Week 24, full compliance with HEP was maintained in 20/30 (65%) patients in CR group and 9/30 (30%) patients in HEP group (p<0.001).

TABLE 2
Changes in fitness parameters at different time points

Variable	Groups	Baseline Mean±SD	Baseline Min-Max	10th weeks Mean±SD	10th weeks Min-Max	24th weeks Mean±SD	24th weeks Min-Max	Time p	Group p	Group × time interaction p
MET (mL/min/kg)	Cardiac rehabilitation	3.8±0.9	2.6-4.9	4.8±1	3.4-6.1	4.3±0.8	3.2-5.5	<0.001	0.004	0.001
	Home exercise	3.7±0.9	2.3-4.7	3.6±0.9	2.4-4.6	3.6±0.9	2.3-4.5			
VO$_2$ max (mL/min/kg)	Cardiac rehabilitation	13.2±3.2	9.6-16.9	16.6±3.7	12.1-19.6	14.9±2.8	11.3-18.1	<0.001	0.003	<0.001
	Home exercise	12.8±3	8.9-16.1	12.5±3	8.3-15.5	12.5±3.2	9-15.9			
Maximum energy consumption (kcal/min)	Cardiac rehabilitation	5.1±1	3.9-6.3	6.4±1.2	5-7.7	5.8±1	4.6-7.3	<0.001	0.006	0.001
	Home exercise	5.1±1	3.6-6.1	5±1.1	3.8-6.3	5±1.2	3.7-6.4			
Maximum load (watt)	Cardiac rehabilitation	61.8±12.3	46.1-74.8	81.7±13.3	55-86.3	72±13.8	50.3-88.5	<0.001	0.002	<0.001
	Home exercise	59.7±10	43.4-71.5	58.6±10.1	43.8-69.4	72±13.8	50.3-88.5			
6 minute walking test (meter)	Cardiac rehabilitation	499.2±52	442-554	588±58.3	517.5-679	581.1±57.4	508-638	<0.001	<0.001	<0.001
	Home exercise	469±51.8	402-531	474.1±50.1	418-545	467.9±53.9	395-516			

SD: Standard deviation; Min: Minimum; Max: Maximum; MET: metabolic equivalent of task; VO$_2$max: maximum oxygen uptake; The Brunner-Langer test (non-parametric repeated measures analysis of variance) was implemented to investigate group-time interactions and effects between groups and times. A significant difference to baseline p<0.05.

TABLE 3
Changes in functional scores and DAS28 at different time points

Variable	Groups	Baseline Mean±SD	10th weeks Mean±SD	24th weeks Mean±SD	Post-hoc Tukey HSD p	Group × time interaction p
SF-36 physical function subscale	Cardiac rehabilitation	43.3±10.5	60±12.1	55±15.1	Baseline vs. 10th week: <0.015	0.039
	Home exercise	50.3±10.8	55±11.4	55±13.1	Baseline vs. 24th week: 0.157	
SF-36 physical role subscale	Cardiac rehabilitation	30±10.2	66.3±20	52.5±16.5		0.059
	Home exercise	21.3±7.7	33.8±8.5	36.3±11.7		
SF-36 pain subscale	Cardiac rehabilitation	38.7±9.1	57.2±10.5	47.3±10.2	Baseline vs. 10th week: <0.001	<0.001
	Home exercise	44.8±10.4	47±11.4	44.4±9.1	Baseline vs. 24th week: 0.029	
SF-36 general health perception subscale	Cardiac rehabilitation	44.4±11.5	50±13.9	46.2±12.5		0.188
	Home exercise	39.5±9.5	37.1±8.9	40.6±10.2		
SF-36 vitality subscale	Cardiac rehabilitation	42.5±10.1	51.3±9.3	50.3±10.7	Baseline vs. 10th week: 0.001	0.008
	Home exercise	49.5±8	44.5±7.8	45.5±8.8	Baseline vs. 24th week: 0.021	
SF-36 social function subscale	Cardiac rehabilitation	62.1±13.5	72.5±12.4	66.9±16.7		0.113
	Home exercise	60±14.9	58.8±9.9	63.8±11.8		
SF-36 emotional status subscale	Cardiac rehabilitation	42.2±9.8	65±13.3	61.7±16.3		0.089
	Home exercise	40±11.3	37±10	40±12.7		
SF-36 mental status subscale	Cardiac rehabilitation	59.8±15.7	60±19.3	62.3±20.4		0.543
	Home exercise	60±13.2	56.6±15	57.8±16		
HAQ score	Cardiac rehabilitation	1.3±0.4	0.8±0.3	0.9±0.4	Baseline vs. 10th week: <0.001	<0.001
	Home exercise	1.1±0.3	1.3±0.5	1.3±0.4	Baseline vs. 24th week: <0.001	
Beck depression inventory	Cardiac rehabilitation	17.5±6.4	11.5±4.1	14.6±5.7	Baseline vs. 10th week: 0.016	0.025
	Home exercise	15.2±4.2	14.60±5.1	14.6±4.8	Baseline vs.24th week: 0.315	
DAS28 score	Cardiac rehabilitation	4±0.4	3.1±0.4	3.5±0.8	Baseline vs. 10th week: <0.001	<0.001
	Home exercise	4±0.5	4.1±0.5	4.2±0.6	Baseline vs.24th week: <0.001	
Tender joint	Cardiac rehabilitation	3.4±1	1.5±0.3	1.9±0.5	Baseline vs. 10th week: <0.001	<0.001
	Home exercise	3.9±1.3	3.9±1.4	3.5±1	Baseline vs.24th week: 0.019	
Swollen joint	Cardiac rehabilitation	0.3±0.07	0	0.1±0.02		0.133
	Home exercise	0.2±0.04	0.2±0.01	0.2±0.04		
ESR (mm/h)	Cardiac rehabilitation	25.4±7.6	24.1±8.3	30.5±10.2		0.603
	Home exercise	23±6.8	26.9±7.8	31.6±11.8		
Global assessment score	Cardiac rehabilitation	53.50±9.3	28.5±5.5	33±11.6	Baseline vs. 10th week: <0.001	<0.001
	Home exercise	53±11.7	53.50±12	56±14.7	Baseline vs.24th week: <0.001	
C-reactive protein (mg/L)	Cardiac rehabilitation	9.4±3.9	7.5±2.5	8.4±2.3		0.955
	Home exercise	15.1±5.4	13.4±4.5	16.2±6.4		

HSD: Honestly significant difference; SD: Standard deviation; SF-36: Short Form 36; HAQ: Health Assessment Questionnaire; DAS28: Disease Activity Score 28; ESR: Erythrocyte sedimentation rate; P<0.05: Significant group-time interaction and difference to baseline (repeated measures ANOVA). The Tukey HSD method was used to detect where the differences in the time points occurred (baseline vs. Week 10 vs. Week 24).

TABLE 4
Changes in cardiovascular risk factors at different time points

Variable	Groups	Baseline Mean±SD	10th week Mean±SD	24th week Mean±SD	Post-hoc-Tukey HSD p	Group × time interaction p
mSCORE risk profile	Cardiac rehabilitation	4±3	3.4±2	3.4±2.3		
	Home exercise	4.3±3.8	4.5±3.7	4±3		
Systolic blood pressure (mmHg)	Cardiac rehabilitation	132.7±16.2	117.3±17.6	120±16.7	Baseline vs. 10th week: 0.004	0.033
	Home exercise	137.8±17.4	128.7±32.8	131.2±20.6	Baseline vs. 24th week: 0.193	
Total cholesterol/HDL ratio	Cardiac rehabilitation	4±0.5	4.1±0.5	4.2±0.9		0.304
	Home exercise	4.4±1	4.8±1.1	4.7±1.1		
Resting heart rate (bpm)	Cardiac rehabilitation	102.8±7.6	96.1±12.4	93.5±13.3	Baseline vs. 10th week: 0.01	0.049
	Home exercise	102.8±11.7	103.6±13.4	100.6±14.3	Baseline vs. 24th week: 0.077	

HSD: Honestly significant difference; SD: Standard deviation; mSCORE: modified Systematic Coronary Risk Evaluation; HDL: high density lipoprotein; P<0.05: Significant group-time interaction and difference to baseline (repeated measures ANOVA). The Tukey HSD method was used to detect where the differences in the time points occurred (baseline vs. Week 10 vs. Week 24).

DISCUSSION

The present study showed that supervised exercise program improved physical fitness, disease activity, functional outcomes, and SBP and resting HR which could reduce the traditional CVD risk factors, although CVD risk reduction could not be demonstrated according to the mSCORE profile in patients with RA.

Cardiovascular disease complications are the leading causes of mortality in RA.[7] Patients with RA have less physical activity and lower aerobic capacity compared to healthy individuals with similar demographic data.[8] In addition, these patients spend more time for low and moderate activities, and physical inactivity is a well-known risk factor for cardiac diseases.[9] In a meta-analysis by Baillet et al.,[10] aerobic exercises were found to be safe in RA patients and these exercises were associated with significant improvements in the VAS, quality of life, HAQ, and number of involved joints.

In our study, most of the fitness parameters showed similar changes. At Week 10, the changes of MET, VO_2 max, the maximum energy consumption, maximum load, and 6MWT scores were better in CR group than HEP group. This difference could be associated with the compliance problem in HEP group. The patients in CR group also did HEP during Weeks 10 and 24. The compliance problem in CR group during the HEP period was significantly lower than HEP group.

Previous studies have demonstrated the relationship between increased fitness and reduced CVD risk. Myers et al.[21] reported a 12% increase in survival with an increase of 3.5 mL/kg/min for VO_2 max in healthy adults. In another study, an increase of 1 mL/kg/min in VO_2 max related with a 15% decrease in CVD mortality risk.[22] It was also shown that fitness of patients with RA was low and these patients had sedentary lifestyle, despite their awareness of the benefits of physical activity. In these patients, supervised exercise programs seemed to have positive effects on fitness, BP, lipid profile, and inflammation.[23] In our study, an increase of 3.5 mL/kg/min in VO_2 max at Week 10 was detected in all patients in CR group. This amount of improvement was equivalent to 20% improvement in VO_2 max. Our findings, therefore, suggest that these patients would have less CVD mortality, if they continue to exercise regularly.

Furthermore, the functional activity levels are decreased in patients with high disease activity

TABLE 5
Changes in the assessment points (baseline vs. 10th and 24th weeks between two groups

	Cardiac rehabilitation group	Home exercise group	
	Mean±SD	Mean±SD	*p*
Metabolic equivalent of task-10th week (mL/min/kg)	4.7±0.1	3.6±0.1	<0.001
Metabolic equivalent of task-24th week (mL/min/kg)	4.2±0.1	3.6±0.1	<0.001
VO2 max-10th week (mL/min/kg)	16.4±0.5	12.7±0.5	<0.001
VO2 max-24th week (mL/min/kg)	14.7±0.4	12.7±0.4	<0.001
Maximum energy consumption-10th week (kcal/min)	6.4±0.2	5±0.2	<0.001
Maximum energy consumption-24th week (kcal/min)	5.8±0.2	5±0.2	<0.001
Maximum load-10th week (watt)	80.8±2.7	59.5±2.7	<0.001
Maximum load -24th week (watt)	71.1±2.3	58.8±2.3	0.001
Six minute walking test-10th week (meter)	574.3±8.3	487.8±8.3	<0.001
Six minute walking test -24th week (meter)	567.5±8.6	481.4±8.6	<0.001
Short Form 36 physical function subscale-10th week	62.8±4.7	52.2±4.7	0.029
Short Form 36 physical function subscale-24th week	58.4±3.2	51.6±3.2	0.057
Short Form 36 physical role subscale-10th week	63.4±6.9	36.6±6.9	0.009
Short Form 36 physical role subscale-24th week	48.9±7.3	39.9±7.3	0.391
Short Form 36 pain subscale-10th week	59.6±2.1	44.6±2.1	<0.001
Short Form 36 pain subscale-24th week	49.7±2.8	41.9±2.8	0.056
Short Form 36 general health perception subscale-10th week	48.4±3.4	38.6±3.4	0.049
Short Form 36 general health perception subscale-24th week	44.3±3.5	42.5±3.5	0.721
Short Form 36 vitality subscale-10th week	53.9±2.4	41.9±2.4	0.001
Short Form 36 vitality subscale-24th week	52.7±3.3	43.1±3.3	0.047
Short Form 36 social function subscale-10th week	72±3.9	59.3±3.9	0.028
Short Form 36 social function subscale-24th week	66.2±4.3	64.4±4.3	0.771
Short Form 36 emotional status subscale-10th week	64.5±9.8	37.6±9.8	0.009
Short Form 36 emotional status subscale-24th week	61±6.9	40.7±6.9	0.044
Short Form 36 mental status subscale-10th week	60±3.5	56.5±3.5	0.492
Short Form 36 mental status subscale-24th week	62.3±3	57.7±3	0.293
Health Assessment Questionnaire score-10th week	0.7±0.1	1.3±0.1	<0.001
Health Assessment Questionnaire score-24th week	0.8±0.1	1.4±0.1	<0.001
Beck depression inventory-10th week	10.9±1.2	15.3±1.2	0.017
Beck depression inventory-24th week	13.9±1.2	15.2±1.2	0.45
DAS28 score-10th week	3.2±0.1	4.1±0.1	<0.001
DAS28 score-24th week	3.5±0.1	4.2±0.1	<0.001
Tender joint-10th week	1.6±0.2	3.7±0.2	<0.001
Tender joint-24th week	2.1±0.3	3.4±0.3	0.003
Swollen joint-10th week	0±0.1	0.2±0.1	0.013
Swollen joint-24th week	0.1±0.1	0.2±0.1	0.462
Erythrocyte sedimentation rate-10th week (mm/h)	23.8±2.9	27.2±2.9	0.395
Global assessment score-10th week	28.3±2.4	53.7±2.4	<0.001
Global assessment score-24th week	32.8±3.1	56.2±3.1	<0.001
C-reactive protein-10th week (mg/L)	9.1±2.2	11.6±2.2	0.426
C-reactive protein-24th week (mg/L)	10±4.7	14.6±4.7	0.498
mSCORE risk profile-10th week	3.6±0.3	4.4±0.3	0.034
mSCORE risk profile-24th week	3.5±0.3	3.9±0.3	0.396
Systolic blood pressure-10th week (mmHg)	119±2.7	133±2.7	0.001
Systolic blood pressure-24th week (mmHg)	121.9±3.2	129.3±3.2	0.109
Total cholesterol/HDL ratio-10th week	4.2±0.2	4.7±0.2	0.09
Total cholesterol/HDL ratio-24th week	4.4±0.2	4.5±0.2	0.587
Resting heart rate-10th week (bpm)	96.4±1.8	103.2±1.8	0.011
Resting heart rate-24th week (bpm)	93.7±2.5	100.3±.5	0.075

Results are given in mean ± standard errors after Bonferroni adjustment analysis of covariance (ANCOVA) is used to detect where the differences in the time points (baseline vs. Weeks 10 and 24) between two groups. A significant difference to baseline p<0.05; VO2 max: Maximum oxygen uptake; DAS28: Disease Activity Score 28; mSCORE: modified Systematic Coronary Risk Evaluation; HDL: High density lipoprotein.

according to previous studies.[24] In our study, HAQ scores were at a level of 1.3 in CR group and in 1.1 HEP group. These scores can be associated with the high ratio of disability of the patients at the beginning of the study. In addition, CR was found to be effective in reducing the levels of disability. At Week 10, the score was 0.78 and at Week 24, the score was redounded to levels of 0.86. On the other hand, there was a non-significant worsening in HEP group. Our results are consistent with the findings of previous studies. In a study by Stavropoulos-Kalinoglou et al.,[20] VO_2 max of patients in aerobic exercise program increased by 10% and 17% at three and six months, respectively. The HAQ scores also reduced from level of 1.4 to 1.0 value after three months with high-intensity aerobic exercise program. In the control group, worsening HAQ scores were observed, consistent with our findings. In another study with RA patients, van Rensburg et al.[25] found a significant improvement in DAS28 scores, although HAQ scores were similar between the groups. The aforementioned study yielded important results including improvements in subscales of SF-36 such as physical functioning, physical role difficulty and pain in CR group. A decrease in the degree of perceived pain and increase of function in CR group provided improvement in these parameters.

In a meta-analysis by Kelley et al.,[26] significant positive effects of exercise on depressive symptoms, anxiety, pain, quality of life, VO_2 max, lower extremity muscle strength and balance were demonstrated. In our study, we also had similar results. In the beginning of the study, CR group had moderate depression scores and, at Week 10, they had mild depression scores. The DAS28 scores significantly decreased over time in CR group. An improvement in DAS28 scores of ≥0.6 was detected in 65% of the patients in CR group and 15% of the patients in HEP group. This change was related to the decrease in the tender joint count and global disease assessment. Although there was a statistically significant decrease in the ESR values in CR group, there was no difference regarding the CRP values overtime between the groups. Therefore, we could not conclude that the improvement in DAS28 was related with the reduction of inflammation. We believe that there is an effect of exercise on inflammation, although we are unable to demonstrate it using traditional methods. Similarly, according to previous literature, anti-inflammatory effect of exercise was found to be associated with reduction in the visceral fat mass, interleukin (IL)-1 receptor antagonist and increase in IL-10 levels.[27]

In the present study, our primary aim was to show the effect of exercise on CVD risk reduction. The Framingham risk score and Heart Score Program were used for the calculation of 10-year fatal CVD risk in patients with RA.[23,28] Recently, the SCORE Risk Index has been recommended by the EULAR guidelines for RA-specific CVD risk calculation.[8] It was modified with multiplier factors. We used the mSCORE method in our study and the median value was ≥3 in 50 of 60 patients. In a study by Rosales-Alexander et al.,[29] the mean score, which was calculated with mSCORE calculation, was reported to be 3.3±4 and the median value was also 3. It was also reported that 74% of patients in the Spanish population had a higher value. These results are consistent with our study results. However, we were unable to demonstrate a risk reduction according to mSCORE, although the patients had improvements in fitness, disease activity, and functional outcome parameters.

On the other hand, there are certain controversies regarding the use of SCORE. In a study by Gómez-Vaquero et al.,[30] multiplier factors consisting of the ACPA and RF levels, RA duration and extra-articular involvement caused a 1.5-fold increase in the SCORE, however, it did not yield a statistically significant difference in the CVD risk estimation. In another study, carotid intima-media thickness and plaque in the carotid artery were not found to be correlated with their SCORE points of the RA patients.[31] In addition, DM, previous heart disease, family history, presence of metabolic syndrome, obesity, and CRP values were not considered multiplying factors. In our study, only two measurements might have influenced the mSCORE calculation: SBP and lipid profile. Although SBP decreased in CR group, TC/HDL ratio remained unchanged, which can be explained with the short duration of follow-up. Altered SBP did not lead to a major change in the calculation of SCORE and, therefore, we were unable to demonstrate a risk reduction in the mSCORE.

This study has certain limitations. The main limitation is the discrepancy of compliance between the groups with an extremely low compliance level in the HEP patients. Second, RA is a multifactorial disease, and that the genetic factors predisposing to inflammation were not investigated in our study. Third, the effect of exercise on inflammation was unable to be evaluated with objective biochemical markers. In addition, it was a single-center study with

a limited sample size. Finally, our study included a selected patient population with RA who had moderate disease activity. Therefore, these results cannot be extrapolated to all patients with RA.

In conclusion, our study results suggest that supervised exercise program cannot reduce CVD risk as assessed by the mSCORE, although it improves physical fitness, disease activity, and functional outcomes which may reduce traditional CVD risk factors in patients with RA. We strongly encourage the development of sensitive outcomes measures in this patient population.

Declaration of conflicting interests

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