Původní sdělení | Original research article

The Effect of Exercise-Based Cardiac Rehabilitation on Neutrophil to Lymphocyte Ratio in Patients with Coronary Artery Disease

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ARTICLE INFO

Article history:
Submitted: 3. 4. 2022
Revised: 24. 6. 2022
Accepted: 14. 7. 2022
Available online: 17. 2. 2023

Klíčová slova:
Poměr počtu neutrofilů k lymfocytům
Zátěžová kardiorehabilitace

SOUHRN

Cíl: Vliv zátěžové kardiorehabilitace (cardiac rehabilitation, KR) na systémový zánět dosud nebyl u pacientů s ischemickou chorobou srdeční (ICHS) podrobněji zkoumán. Jako nový marker zánětu byl navržen poměr počtu neutrofilů a lymfocytů (N/L), přičemž se ukázalo, že jeho zvýšené hodnoty jsou u pacientů s ICHS spojeny s nepříznivějším výsledným klinickým stavem. Dalším nezávislým prediktorem morbidity a mortality je u pacientů s ICHS nízká kvalita života v souvislosti se zdravím (health-related quality of life, HRQL). Cílem této studie bylo zjistit vliv zátěžové KR na poměr N/L a na HRQL u pacientů s ICHS.
Metody: Do studie jsme zařadili 200 ambulantních pacientů se stabilní ICHS indikovaných svými lékaři k absolvování III. fáze programu KR (skupina KR). Tuto skupinu jsme srovnali se skupinou 100 ambulantních pacientů se stabilní ICHS bez přístupu ke KR pro velkou dojezdovou vzdálenost nebo komorbidity omezující možnost zátěže (skupina bez KR).
Výsledky: Nebyl nalezen žádný statisticky významný rozdíl mezi skupinami ve vstupních klinických a biochemických charakteristikách. I když poměr N/L a hodnoty CRP po programu KR byly nižší než poměr N/L a hodnoty CRP před absolvováním programu KR ve skupinách KR a bez KR ($p < 0{,}001$ a $p < 0{,}007$, resp. $p < 0{,}001$ a $p < 0{,}001$), byl poměr V/L a hodnoty CRP ve skupině KR po absolvování programu KR nižší než ve skupině bez KR ($p < 0{,}001$ a $p < 0{,}001$, resp. $p < 0{,}001$ a $p < 0{,}001$). Celková skóre HRQL v dotazníku MacNew byla po absolvování KR vyšší ve skupině bez KR ($p < 0{,}001$).
Závěry: Program zátěžové KR zlepšuje u pacientů se stabilní ICHS poměr N/L a zvyšuje HRQL. Protože léčba tlumící systémový zánět pozitivně ovlivňuje výsledný stav pacientů s ICHS, mohou být naše zjištění potenciálně významná pro klinickou praxi.

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Keywords:
Exercise-based cardiac rehabilitation
Neutrophil/lymphocyte ratio

ABSTRACT

Objectıve: The effect of exercise-based cardiac rehabilitation (CR) on systemic inflammation was not well established in patients with coronary artery disease (CAD). Neutrophil/lymphocyte (N/L) ratio has emerged as a new inflammation marker and elevated levels were found to be associated with worse clinical outcome in patients with CAD. Also, poor impaired health-related quality of life (HRQL) is an independent predictor of morbi-mortality in patients with CAD. The purpose of this study is to determine the effect of exercise-based CR on N/L ratio and HRQL in patients with CAD.
Methods: We enrolled 200 stable CAD out-patients referred for Phase III CR program by their physicians (CR group). We compared them with 100 stable CAD out-patients who did not have access to CR because of travel distance or comorbid conditions that limited exercise (non-CR group).
Results: There was not a statistically significant difference in the baseline clinical and biochemical characteristics between the groups. Although N/L ratio-post and CRP-post values were lower than the N/L ratio-pre and CRP-pre in CR & non-CR groups (p <0.001 & p: 0.007 and p <0.001 & p <0.001), in the CR group N/L ratio--post and CRP-post values were lower than the non-CR group (p <0.001 & p <0.001 and p <0.001 & p <0.001). Mac-New HRQL total-postscores were higher in the non-CR group (p <0.001).
Conclusions: Exercise-based CR program improves N/L ratio values and HRQL in patients with stable CAD. A therapy that improves systemic inflammation is important for good outcome in patients with CAD, therefore our results may have potentially significant clinical effects.

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DOI: 10.33678/cor.2022.081

Please cite this article as: Kara F, Özderya A, Uzun G, et al. The Effect of Exercise-Based Cardiac Rehabilitation on Neutrophil to Lymphocyte Ratio in Patients with Coronary Artery Disease. Cor Vasa 2023;65:39–44.

Introduction

Inflammation plays an important role in the progression and destabilization of atherosclerosis.[1] White blood cells, particularly neutrophils, are useful inflammatory biomarkers associated with cardiovascular events.[2] On the other hand, low lymphocyte counts have been shown in acute coronary syndrome patients and associated with various complications.[3] Recently, the absolute number of neutrophils to the number of to lymphocytes (neutrophil/lymphocyte (N/L) ratio) has emerged as a new inflammation marker. Previous studies have shown that N/R ratio elevation was associated with the presence and the severity of coronary artery disease (CAD), poor prognosis in acute coronary syndromes and stable coronary heart diseases can be used in the risk stratification of patients with various cardiovascular (CV) diseases in addition to the traditionally used markers.[3–5]

Exercise-based cardiac rehabilitation (CR) is a comprehensive intervention including medically supervised exercise training, risk factor management, patient education, and psychosocial counseling.[6] CR has been reported to be effective in improving exertional ischemic symptoms, exercise tolerance, and coronary risk factors in patients with CAD. Also, it was shown that exercise-based CR reduces total and CV mortality in ranging rate from 20% to 32% in patients with CAD.[7] Although the anti-inflammatory effects of exercise training have been reported,[8] the effect of this therapy on systemic inflammation was not well established in patients with CAD.

Patients with CAD are likely to have an impaired health-related quality of life (HRQL)[9] and poor HRQL is an independent predictor of morbi-mortality in patients with CAD.[10] So, the assessment of HRQL is increasingly important in evaluating the effectiveness of CAD treatment strategies.[11]

The purpose of this study is to determine the effect of exercise-based CRprogramon N/L ratio, which is a new, inexpensive, easy obtain and widely available inflammation marker, in patients with stable CAD. Also, we analyzed the effect of CR program on HRQL in these patients. This study has potential important clinical implications as epidemiologic data strongly support the persistent low-level inflammation as an independent predictor of coronary heart diseases[12] and the identification of therapies that improves systemic inflammation is important for prevention of CV events.

The study protocol did approve by the local Ethics Committee of the University of Health Sciences Trabzon Kanuni Training and Research Hospital and the Republic of Turkey Ministry of Health. The study was conducted in concordance with the Helsinki Declaration and the International Conference on Good Clinical Practices Harmony, and written informed consent was obtained from all participants.

Methods

Study population

We enrolled 230 stable CAD out-patients referred for Phase III CR program by their physicians. 30 patients did not complete the CR program due to personal reasons, so finally 200 stable CAD out-patients were included in the CR group. We compared them 100 stable CAD out--patients who did not have access to CR because of travel distance or comorbid conditions that limited exercise (non-CR group, standard pharmacological care alone). Study inclusion criterions were: age between 18–80 years; left ventricular ejection fraction >45%; coronary angiographic documentation of CAD which was defined as having more than 70% stenosis in at least one coronary artery. Patients with immunologic or inflammatory disease, hematological disease, sepsis, active local or systemic infections, chronic renal disease (creatinine >1.6 mg/dL), a history of recent infection (<3 months before the study) and a history of malignancy were excluded.

Patients' medical treatments were optimized before the participation and none had any medication changes throughout the study.

Blood measurements were made at baseline for non-CR group, one day before the CR program for CR-group and after 6 weeks for both groups. Total and differential leukocyte counts were measured using an automated hematology analyzer Advia 2120 (Siemens). Body mass index (BMI) was calculated as weight (kg)/height (m^2).

CR program

A step incremental cycle ergometer test was performed before the CR program to determine the exercise capacity of the patients. After a 2-minute resting period, the workload was increased by 25 W every 2 minutes. With electrocardiogram monitoring heart rate and blood pressure were measured throughout the exercise. The maximum workload was determined as the maximal exercise capacity.

The CR program was performed on supervising of a multidisciplinary team including a cardiologist, an experienced physiotherapist as a coordinator and a physical therapy and rehabilitation specialist as a medical director. The rehabilitation program was performed in the CR center of our cardiology and cardiovascular surgery hospital.

Main part of the rehabilitation program was aerobic exercise training. According to the result of the exercise testing, the exercise prescription was scheduled individually. Patients continued the program for 5 days in a week, for a total of 6 weeks. Before aerobic exercise muscle training was perfomed by all patients. Each session lasted 30 minutes, which included a 8 warm-up of 5 minutes and a final 5 minute cool-down period. The aerobic exercise intensity was prescribed according to the individual's exercise capacity. Exercise intensity began at 40–50% of maximal heart rate reserve and gradually increased to 70–85% of maximal heart rate reserve. Heart rate reserve was evaluated by the Karvonen Formula (HRtrain = (HRmax – HRrest) × Exercise Intensity + HRrest).[13] HRtrain represents heart rate during the aerobic exercise, HRmax represents maximum heart rate reached thorough the cycle ergometer test, and HRrest represents heart rate at rest. The Borg Scale of Rate of Perceived Exertion (RPE) was used; patients exercised at an RPE of 13–15. Electrocardiograms were continuously tele-monitored and blood pressures were measured every 5 minutes throughout the exercise. During study, pa-

tients were also directed to psychologist, dietitian, and smoking cessation clinic.

Quality of life measures

The Mac-New Heart Disease HRQL questionnaire, which is specifically designed to evaluate how daily activities and physical, emotional, and social functioning are affected by CAD and its treatment, was used in the current study. The-MacNew questionnaire consists of 27 items, which fall into 3 domains:[1] a 13-item scale in the physical limitations domain,2 a 14-item scale in the emotional function domain, and[3] a 13-item scale in the social function domain. There are 5 items that address the impact of symptoms: 1. angina/chest pain, 2. shortness of breath, 3. fatigue, 4. dizziness, and 5. aching legs. Scoring of the Mac New is straight-forward. The maximum possible score in any domain is 7 [high HRQL] and the minimum is 1 [poor HRQL].[14] The time frame for the Mac-New is the previous two weeks. All study participants completed the questionnaire at baseline and after 6 weeks.

Statistical analysis

Statistical analyses were carried out using SPSS statistical software (version 21.0, SPSS, Chicago, IL, USA). Continuous variables are presented as mean and standard deviation. Categorical variables are presented as number and percentage.The Kolmogorov–Smirnov test was used to verify the normality of the distribution of continuous variables. The independent sample t test or the Mann–Whitney U test was used for the continuous variables and the chi-square test for categorical variables. The paired samples T test was used to compare variables before and after therapy. General linear model of repeated measurements test was used for the evaluation of differences in measurements before and after the treatment of patient groups. Pearson correlation analysis was performed to examine the relationship between continuous variables. A p value of <0.05 was considered statistically significant.

Results

The study population consisted of 300 stable CAD patients (200 patients in CR-group and 100 patients in non-CR group). There was not statistically significant difference in the baseline clinical and biochemical characteristics between the groups (Table 1). Majority of patients were hypertensive in both groups (CR-group 91%, non-CR group 85%; p: 0.178). 58% in the CR-group and 62% in the non--CR group had a history of percutaneous coronary intervention (p: 0.535). Changes of the values in CR and non-CR groups were shown in Table 2. Although LDL-cholesterol (mg/dl)-post, triglycerides(mg/dl)-post, N/L ratio-post and CRP (mg/l)-post values were lower than the LDL-cholesterol (mg/dl)-pre, triglycerides(mg/dl)-pre, N/L ratio –pre and CRP mg/l-pre in CR &non-CR groups (p <0.001 & p < 0.001, p <0.001 & p <0.001, p <0.001 & p: 0.007 and p <0.001 & p <0.001 respectively), in the CR group LDL-cholesterol (mg/dl)-post, triglycerides(mg/dl)-post, CRP(mg/l)--post and N/L ratio-post values were lower than in the non-CR group (p <0.001, for all measurements). Pre- and post-N/L ratio values in groups were shown in Figure 1.

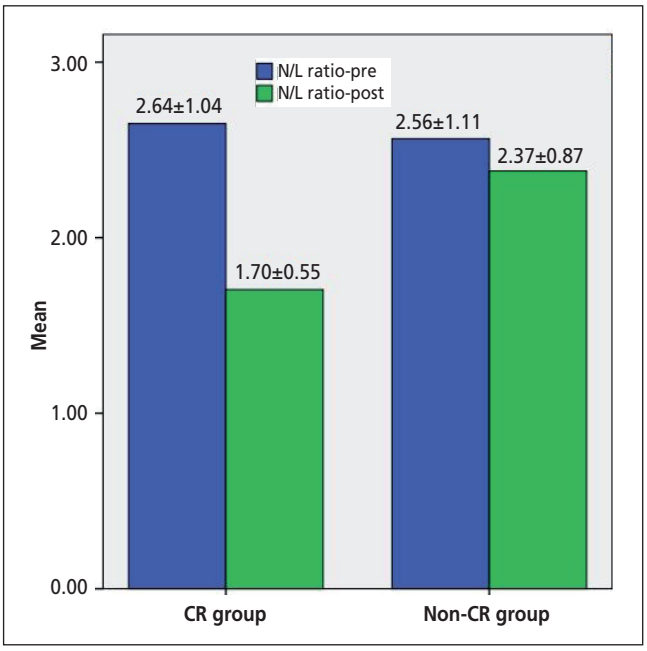

Fig. 1 – Pre- and post-N/L ratio values in groups.

Table 1 – Baseline clinical characteristics and laboratory findings of study participants

Variables	CR group (n: 200)	Non-CR group (n: 100)	p value
Age (years)	56.2±7.9	57.9±7.3	0.073
Sex, female (n, %)	44 (22%)	23 (23%)	0.883
BMI (kg/m^2)	28.3±3.9	28.2±3.1	0.853
Hypertension (n, %)	181 (91%)	85 (85%)	0.178
Diabetes mellitus (n, %)	55 (28%)	20 (20%)	0.203
Current smoker (n, %)	27 (14%)	11 (11%)	0.586
Fast plasma glucose (mg/dL)	107±34	102±27	0.116
Hemoglobin (g/dL)	13.6±1.1	13.4±1.0	0.114
Creatinine (mg/dL)	0.87±0.21	0.89±0.21	0.616
LV ejection fraction (%)	58±6	57±5	0.117
RAS inhibitors (n, %)	162 (81%)	83 (83%)	0.753
Beta-blockers (n, %)	155 (78%)	85 (85%)	0.168
Calcium-channel blockers (n, %)	90 (45%)	43 (43%)	0.806
Statins (n, %)	200 (100%)	100 (100%)	NA
By-pass surgery history (n, %)	37 (19%)	19 (19%)	0.917
PCI history (n, %)	116 (58%)	62 (62%)	0.535
ACS history (n, %)	49 (25%)	29 (29%)	0.406

ACS – acute coronary syndrome; BMI – body mass index; CR – cardiac rehabilitation; LV – left ventricle; PCI – percutaneous coronary intervention; RAS – renin-angiotensin inhibitors.

There was not statistically significant difference in the Mac-New HRQL social-pre, Mac-New HRQL physical-pre, Mac-New HRQL emotional-pre and Mac-New HRQL total-

Table 2 – Changes of the values in the CR and non-CR groups

Variables	CR group (n: 200)	non-CR group (n: 100)	*p* value
LDL-cholesterol (mg/dL)-pre	120±36	117±31	0.835
LDL-cholesterol (mg/dL)-post	92±25	112±25	<0.001
p value	<0.001*	<0.001*	<0.001#
HDL-cholesterol (mg/dL)-pre	35±6	35±5	0.329
HDL-cholesterol (mg/dL)-post	39±6	36±5	<0.001
p value	<0.001*	<0.001*	<0.001#
Triglycerides (mg/dL)-pre	158±62	147±39	0.668
Triglycerides (mg/dL)-post	121±43	137±34	<0.001
p value	<0.001*	<0.001*	<0.001#
WBC count, × 10^9/L -pre	7.56±1.34	7.40±1.03	0.252
WBC count, × 10^9/L -post	6.65±1.30	7.32±1.06	<0.001
p value	<0.001*	0.903*	<0.001#
Neutrophil count, × 10^9/L -pre	4.66±1.17	4.83±1.26	0.475
Neutrophil count, × 10^9/L -post	3.67±0.97	4.56±1.14	<0.001
p value	<0.001*	<0.001*	<0.001#
Lymphocyte count, × 10^9/L -pre	1.94±0.69	2.06±0.58	0.140
Lymphocyte count, ×10^9/L -post	2.28±0.67	2.02±0.50	0.002
p value	<0.001*	<0.429*	<0.001#
N/L ratio-pre	2.64±1.04	2.56±1.11	0.256
N/L ratio-post	1.70±0.55	2.37±0.87	<0.001
p value	<0.001*	0.007*	<0.001#
CRP (mg/L) -pre	3.44±1.32	3.40±1.26	0.792
CRP (mg/L) -post	2.26±0.81	3.33±1.19	<0.001
p value	<0.001*	<0.001*	<0.001#
Mac-New HRQL social-pre	5.14±0.48	5.17±0.51	0.547
Mac-New HRQL social-post	5.87±0.33	5.31±0.50	<0.001
p value	<0.001*	<0.001*	<0.001#
Mac-New HRQL physical-pre	4.99±0.47	4.93±0.41	0.449
Mac-New HRQL physical-post	5.85±0.36	5.08±0.46	<0.001
p value	<0.001*	<0.001*	<0.001#
Mac-New HRQL emotional-pre	4.99±.48	5.08±0.35	0.070
Mac-New HRQL emotional-post	6.05±0.44	5.18±0.37	<0.001
p value	<0.001*	<0.001*	<0.001#
Mac-New HRQL total-pre	4.99±0.34	5.01±0.21	0.158
Mac-New HRQL total-post	5.87±0.24	5.21±0.30	<0.001
p value	<0.001*	<0.001*	<0.001#

*p** value – *p* value within groups (paired samples T test); *p*# value – general linear model repeated measures test.
CR – cardiac rehabilitation; CRP – C-reactive protein; HDL – high density lipoprotein; HRQL – health-related quality of life; LDL – low density lipoprotein; WBC – white blood cell.

pre scores between CR and non-CR groups (*p*: 0.547, *p*: 0.449, *p*: 0.070 and *p*: 0.158, respectively). Although Mac-New HRQL social-post, Mac-New HRQL physical-post, Mac-New HRQL emotional-post and Mac-New HRQL total-post

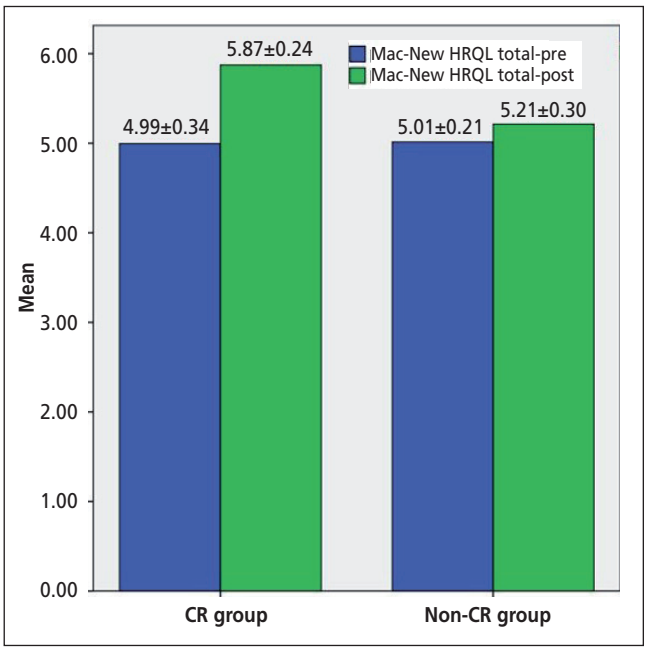

Fig. 2 – Pre- and post-Mac-New HRQL total score values in groups.

scores were higher in the CR & non-CR groups (*p* <0.001 & *p* <0.001 for all measurements), in the CR group Mac-New HRQL social-post, Mac-New HRQL physical-post, Mac-New HRQL emotional-post and Mac-New HRQ total-post scores were higher in the CR-group than in the non-CR group (*p* <0.001 for all measurements). Pre- and post Mac-New HRQL total score values in groups were shown in Figure 2. In the general linear model of repeated measurements test, the change in the parameters in the cardiac rehabilitation group was statistically larger than the group not included in the cardiac rehabilitation (*p* <0.001).

We also analyzed the correlation of decrement in N/L ratio (Δ N/L ratio) withdecrement in CRP (Δ CRP) in CR group. Correlation analyses showed that Δ N/L ratio significantly correlated with Δ CRP (r: 0.529, *p*<0.001).

Discussion

We have demonstrated a significant decrease in N/L ratio values in patients with CAD after participating in an exercise-based CR program compared to those treated with medical therapy alone. This study supports a potential beneficial effect of participation in CR program on lowering N/L ratio levels in patients with CAD. Participation in exercise-based CR program was also found to be associated with improvement in HRQL in these patients.

N/L ratio has recently emerged as a potential new biomarker which singles out individuals at risk for future CV events after controlling for all the currently accepted risk factors and commonly used biomarkers.[3] An observational study in a cohort of patients with CAD demonstrated that atherosclerosis progression correlated with increased N/L ratio values.[15] Arbel et al. demonstrated that N/L ratio >3 was an independent predictor of CAD severity and worse clinical outcome with 3-year follow-up in 3005 patients and these results were found to be independent of

clinical presentation (acute coronary syndrome status, diabetes status, statin use).[3] In a study of 186 patients who presented with stable angina pectoris, the N/L ratio >2.7 was found to be correlated with high SYNTAX score.[16] At another study the N/L ratio found to be good predictor of a high Gensini score and the N/L ratio >2.04 highly predicted the presence of CAD.[15] In our study the N/L ratio was 2.64 in the CR group and 2.56 in the non-CR group. Although there was not standard N/L ratio cut-off value for predicting CAD, our study population had high N/L ratio values in concordance with previous studies.

Previous research provides evidence that a physically active lifestyle is associated with lower whole-body inflammatory biomarkers but a number of researchers report minimal or no anti-inflammatory effect.[8] It was shown that participation in CR appears to independently decrease the level of high sensitive C-reactive protein (HCRP) regardless of gender, age or presence of metabolic syndrome in patients with coronary heart disease.[12] Milani et al. analyzed the effect of 3-month exercise-based CR on HCRP in patients with CAD.[17] They demonstrated a 41% median reduction in levels of HSCRP independent of statin therapy and weight reduction. They speculated that this reduction was of similar or greater magnitude to that observed in multiple studies using statin therapy, where median reduction in HSCRP was reported to be between 15% and 20%.[17] CRP is a well-studied inflammation marker and elevated levels were associated with adverse CV events/poor prognosis in patients with CAD.[12] In this study we also analyzed the effect of exercise-based CR program on CRP values. In concordance with previous studies we found that patients who participated CR had lower CRP levels than those treated with medical therapy alone. We demonstrated 34.6% reduction in N/L ratio values and 34.3% reduction in CRP values in patients who participated CR program. Our study population was under statin treatment. So we showed the additive anti-inflammatory effect of exercise-based CR program on the well-proven benefits of statin therapy.

Also N/L ratio-post and CRP-post values were found to be lower than N/L ratio-pre and CRP-pre values in both groups. This may be explained by the fact that participants medical treatments were optimized before being included in the study. But between CR and non-CR groups N/L ratio-post and CRP-post values were found to be significantly lower in the CR-group.

We implemented the CR program for 5 days a week for a total of 6 weeks. Wang et al. showed in their study that participants exhibited a significant decrease in N/L ratio values with 4-week exercise training, which was shorter than our program, in 43 overweight male adolescents.[18] Although previously it was shown that the anti-inflammatory effect of exercise training was evident as little as 2 to 12 weeks of supervised exercise,[8] if we used 3-month program we may had lesser N/L ratio values.

Neuro-inflammation plays an important role in depression, anxiety, irritability, and mood instability.[19,20] Previously it was shown that aerobic exercise improves quality of life, psychological well-being, and systemic inflammation in subjects with Alzheimer's disease.[20] Peixoto et al.[21] demonstrated that exercise based-CR improves HRQL in 45 patients with acute myocardial infarction. Johnson et al.[10] showed in their multi-center study that CR improves HRQL in women CAD patients. Our study population was larger than in these studies and we analyzed patients with stable CAD. In concordance with these studies we showed that exercise based-CR improves HRQL in patients with stable CAD that may be related with anti-inflammatory effect of CR. We used Mac-New HRQL questionnaire, because it has already been demonstrated to be valid, reliable and responsive in patients with CAD.[22]

Our results are in agreement with other studies that have shown that exercise-based CR program reduces LDL-cholesterol, triglyceride levels, and increased HDL-cholesterol levels.[7,23]

CR program composed of structured exercise training and comprehensive education addressing cardiac risk. Participation has been shown to reduce CV mortality, need for re-hospitalization and re-vascularization procedures and lead to improve functional status when compared with usual care.[24–26] Currently the major problem with exercise based-CR is its underutilization by physicians. On the other hand, although data supporting the benefits of CR are highly regarded, they lack the support of large, appropriately powered clinical trials.[27] Therefore randomized controlled trials are needed to assess the impact of CR in CAD patients with a higher risk and patients with SAP.[28] By showing the positive effect of exercise-based CR program on systemic inflammation and HRQL, we think that our study can provide asignificant contribution to the literature.

Study limitations

This study has several limitations. Our study was not randomized, raising the possibility of selection bias; particularly the control population chose not to attend the exercise-based cardiac rehabilitation program. We implemented the CR program for 5 days a week for a total of 6 weeks. We could implement a longer CR program, but there is no clear exercise duration or exercise intensity recommended in previous studies or reviews. Since our results are positive, we think this period is enough. We do not use spiroergometry.

Conclusion

In conclusion, this study provides new data on the effect of exercise-based CR program on the N/L ratio values. We showed that exercise-based CR program improves N/L ratio values and HRQL in patients with stable CAD. N/L ratio, an inflammatory biomarker, can be of predictive and prognostic factor for CV events and therapies that improves systemic inflammation is important for good outcome in patients with CAD.

Acknowledgements
None declared.

Conflicts of interest
None declared.

Funding sources
None declared.

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