



Original/Deporte y ejercicio

## Effects of exercise on inflammation in cardiac rehabilitation

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### Abstract

**Background:** programs of weight loss and a healthy diet are recommended for patients with cardiovascular risk but the effectiveness of these programs in decreasing cardiovascular mortality is controversial.

**Aim:** to examine the acute and long-term effects of a 2-month cardiac rehabilitation program on chemokines related to inflammation in subjects with cardiovascular disease.

**Design:** prospective cohort study.

**Methods:** twenty-six patients with cardiovascular disease enrolled in a cardiac rehabilitation program based on nutritional and exercise interventions were studied. Lifestyle and clinical, metabolic and inflammatory variables were analysed.

**Results:** 88.5% were men and the mean age was  $54.9 \pm 7.8$  years. At the end of the cardiac rehabilitation program the levels of carbohydrate and lipid metabolism were lower, except for high density lipoprotein cholesterol which was higher. The levels of uric acid, interleukin-6, interleukin-1Beta, adiponectin and leptin remained stable. Interleukin-6 correlated positively with levels of C-reactive protein and negatively with blood glucose. Interleukin-1Beta correlated positively with C-reactive protein levels and negatively with blood pressure figures. Significant correlations were seen between the changes in levels of interleukin-6 and interleukin-1Beta and changes in metabolic equivalents, and in C-reactive protein levels before and after the cardiac rehabilitation program. No significant correlations were observed with weight, waist circumference or fat mass.

**Conclusions:** a cardiac rehabilitation program decreased anthropometric variables and blood pressure figures.

### EFFECTOS DEL EJERCICIO SOBRE LA INFLAMACIÓN EN REHABILITACIÓN CARDÍACA

#### Resumen

**Introducción:** a los pacientes con riesgo cardiovascular se les recomiendan programas de pérdida de peso y dieta saludable, pero la eficacia de estos programas a la hora de reducir la mortalidad es controvertida.

**Objetivo:** examinar los efectos agudos y a largo plazo de un programa de rehabilitación cardíaca de dos meses de duración sobre las quemocinas relacionadas con la inflamación en pacientes con enfermedad cardiovascular.

**Diseño:** estudio de cohortes prospectivo.

**Métodos:** se estudiaron 26 pacientes con enfermedad cardiovascular inscritos en un programa de rehabilitación cardíaca basado en intervenciones nutricionales y de ejercicio. Se analizaron el estilo de vida y variables clínicas, metabólicas e inflamatorias.

**Resultados:** 88,5% eran hombres y la edad media fue de  $54,9 \pm 7,8$  años. Al final del programa de rehabilitación cardíaca las variables del perfil glucémico y lipídico descendieron, excepto el colesterol de lipoproteínas de alta densidad, que aumentó. Ácido úrico, interleucina-6, interleucina-1 beta, adiponectina y leptina se mantuvieron estables. Interleucina-6 correlacionó positivamente con proteína C reactiva y negativamente con glucosa en sangre. Interleucina-1 beta correlacionó positivamente con proteína C-reactiva y negativamente con las cifras de presión arterial. Encontramos correlaciones significativas entre los cambios en interleucina-6 e interleucina-1 beta y los cambios en los equivalentes metabólicos y proteína C-reactiva, antes y después del programa de rehabilitación cardíaca. No se observaron correlaciones significativas con peso, circunferencia de cintura o masa grasa.

**Conclusiones:** la rehabilitación cardíaca mejora las variables antropométricas, las cifras de presión arterial,

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Recibido: 18-II-2015.

Aceptado: 14-III-2015.

res, and improved lipid metabolism and ergometry data. However, no changes regarding the inflammatory state were observed.

(*Nutr Hosp.* 2015;31:2633-2640)

DOI:10.3305/nh.2015.31.6.8868

Key words: *Cardiovascular disease. Weight loss. Healthy diet. Cardiac rehabilitation program. Chemokines.*

## Abbreviations

AMI: acute myocardial infarction.  
BMI: body mass index.  
CVD: cardiovascular disease.  
HbA1c: glycated haemoglobin.  
HDL: high density lipoprotein.  
IL-6: interleukin 6.  
IL-1 $\beta$ : interleukin 1 $\beta$ .  
IPAQ: International Physical Activity Questionnaire.  
LDL: low density lipoprotein.  
MCP-1: monocyte chemoattractant protein-1.  
METs: metabolic equivalents.  
PVD: peripheral vascular disease.  
SD: standard deviation.  
TNF- $\alpha$ : tumour necrosis factor- $\alpha$ .  
VCAM-1: vascular cell adhesion molecular-1.  
WC: waist circumference.

## Background

A progressive distancing from Mediterranean diet has been observed with more overweight and obesity and, therefore, higher risk of cardiovascular disease (CVD)<sup>1</sup>. Events arising from CVD are caused by an atherosclerotic process. It is well known that the addition of physical exercise to hypocaloric treatments produced greater fat mass and weight loss than dieting alone<sup>2</sup>. Exercise is known to prevent plaque development and induce the regression of vascular stenosis. Exercise asserts this atheroprotective role by reducing or preventing oxidative stress and inflammation through various pathways<sup>3</sup>. In addition, exercise improves insulin action in the immediate post-exercise period, though the mechanism is unclear<sup>4</sup>. Low muscle condition has been associated with less healthy clinical, lipid and metabolic profile revealing the importance of training as indicator of cardiovascular health<sup>5</sup>. Research has suggested that changes in diet and exercise, even if only modest weight loss is reached, improve insulin sensitivity and decrease blood pressure, lipids and inflammatory cytokines levels<sup>6</sup>. Nevertheless, a recent study found that an intensive lifestyle intervention based on reduced calorie intake and increased physical activity for 10 years did not reduce the risk of cardiovascular morbidity or mortality, as compared with a control program of diabetes support and education, among overweight or obese patients with type 2 diabetes<sup>7</sup>.

así como el perfil de lípidos y los resultados de la ergometría. Sin embargo, no se observaron cambios con respecto al estado inflamatorio.

(*Nutr Hosp.* 2015;31:2633-2640)

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Palabras clave: *Enfermedad cardiovascular. Pérdida de peso. Dieta sana. Programa de rehabilitación cardiaca. Quemocinas.*

There are pro-inflammatory factors linked to atherosclerosis such as interleukin 6 (IL-6)<sup>3</sup>. Recently, IL-6 has been recognized as the predominant exercise cytokine. It is released by the muscle in response to contractions<sup>8</sup>. The pathological versus beneficial role of IL-6 remains unclear. On one hand, increased IL-6 in obesity is associated with the physiopathology of type 2 diabetes, while on the other hand muscle-derived IL-6 seems to increase glucose uptake and fat oxidation in skeletal muscle and improve glucose tolerance and insulin sensitivity<sup>4</sup>. Ellingsgaard *et al.*<sup>9</sup> found that IL-6, released from either contracting skeletal muscle or white adipose tissue, enhances insulin secretion by increasing glucagon-like peptide-1 secretion from intestinal L cells and pancreatic alpha cells. Other authors have suggested that IL-6 could exert modulatory effects during exercise<sup>10</sup>. Interleukin 1 $\beta$  (IL-1 $\beta$ ) is another inflammation chemokine related to the metabolic syndrome<sup>11</sup>.

The purpose of this study was to examine the effects of a 2-month cardiac rehabilitation program on chemokines related to inflammation in subjects with CVD.

## Materials and methods

### Study Population

We conducted a longitudinal prospective study, involving 26 patients enrolled in a cardiac rehabilitation program after an acute cardiac event during 2010. The candidates were informed of the characteristics and objectives of the study before they signed an informed consent. The inclusion criteria were: provision of informed consent, suitable cardiac diagnosis, clinically stable patients, and a life expectancy of at least one year. Exclusion criteria included: age less than 18 or more than 80 years, and the presence of acute or chronic inflammatory disease, infectious disease, metastatic disease, or psychological disease.

### Cardiac rehabilitation program

The program was carried out according to the protocol approved by the Ethics Committee of our Hospital and conformed to the guidelines of the Helsinki protocol.

**Rehabilitation intervention:** The program included early mobilization, respiratory exercises, prevention of complications and basic information about heart disease. Two months after hospital discharge, we checked for clinical and risk factors at a specialized outpatient office and physical training for 8 weeks, psychological treatment by relaxation techniques, and a health education program were carried out. The health education program consisted of talks about theoretical and practical aspects of CVD. The exercises were performed 3 times a week. The physical training consisted of warming up, aerobic exercise and cooling down / relaxation phases. Stretching and exercises with free weights (1-2 kg) were performed in the warming-up phase for 20 minutes. Then, treadmill or bicycle aerobic exercise was performed for 30 minutes. Finally, walking and breathing exercises were performed in the cooling-down phase for 10 minutes. An ergometry test was performed before and after the cardiac rehabilitation program.

**Nutritional intervention:** A Mediterranean diet was recommended, encouraging a low calorie and fat diet, and higher consumption of oleic and omega-3 acids, which are associated with a better cardiovascular profile. The dietary intervention included a reduction of 500-600 kilocalories per day with 50% carbohydrates, 30% fats and 15-20% proteins. In addition, a review of the diabetes education of the patients with diabetes was performed.

#### *Study variables*

At the first (baseline) visit we reviewed the inclusion and exclusion criteria and obtained demographic data as well as information about the main diagnosis, associated disorders, pharmacological treatment and physical activity using the International Physical Activity Questionnaire (IPAQ)<sup>12</sup>. Eating habits were recorded using an adaptation of the Trichopoulou scale, a validated extensive semi-quantitative questionnaire on food intake, which indicates the degree of adherence to the traditional Mediterranean diet<sup>13</sup>. The physical examination included data for weight, height, body mass index (BMI), waist circumference (WC) and single frequency impedance (Bio-medica®). We collected the data before the acute cardiac event (retrospectively), and before and at the end of the cardiac rehabilitation program, as well as 12 months later.

#### *Laboratory determinations*

Following a minimum 8-h fast venous blood samples were drawn for biochemical analyses at three times: before and at the end of the cardiac rehabilitation program, as well as 12 months later. Samples were centrifuged at 4000 rpm for 15 minutes at 4 C°. Plasma and serum were aliquotted and stored at -80 C° until

analysis. The biochemical variables were measured using standard enzymatic methods. The plasma adipokine levels were measured using manual commercial kits. Human IL-6 Quantikine ELISA Kit from R&D Systems (Abingdon, United Kingdom) for IL-6 levels, Human IL-1 beta/IL-1F2 Quantikine HS ELISA Kit from R&D Systems (Abingdon, United Kingdom) for IL-1 $\beta$  levels, ELISA kits (DRG Diagnostics, Marburg, Germany) for adiponectin levels, and ELISA kit from Mediagnost (Reutlingen, Germany) for leptin levels, according to the manufacturer's instructions, respectively.

#### *Statistical analysis*

Descriptive statistics included mean, standard deviation (SD), and ranges for quantitative variables, and percentages for qualitative variables. Information from each visit was compared by the Mann Whitney U and the Friedman test for non-parametric variables. The Wilcoxon test for paired samples was used to compare different times (Bonferroni correction was applied). A level of  $p < 0.05$  was accepted as being statistically significant.

## **Results**

We studied 26 patients, 88.5% men and with a mean age of  $54.9 \pm 7.8$  years. The most frequent cardiac event leading to inclusion in the cardiac rehabilitation program was acute myocardial infarction (AMI) with stent implantation (47.1%). Other cardiac events included angina with stent 24.1%, coronary bypass 20.2% and AMI without stent 8.6%. A previous cardiac event was present in 42.3% of the patients.

Ergometry data before and after the rehabilitation program were obtained (Table I). Significant differences were found in tolerated exercise time ( $6.1 \pm 2.3$  vs.  $7.3 \pm 3$  minutes;  $p = 0.006$ ), metabolic equivalents (METs) ( $7.4 \pm 2.3$  vs.  $8.2 \pm 2.8$ ;  $p = 0.045$ ), and Börg's perceived exertion scale ( $11.7 \pm 1.5$  vs.  $13.6 \pm 1.3$ ;  $p < 0.001$ ), which improved after the rehabilitation program.

Demographic and clinical variables at the beginning, at the end, and 12 months after the cardiac rehabilitation program are shown in table II and figures 1 and 2. Anthropometric variables, fat mass, and blood pressure decreased at the end of the cardiac rehabilitation program but then increased close to baseline levels 12 months later. The changes in waist circumference, fat mass, and systolic blood pressure were significant. The results of the Trichopoulou questionnaire improved after the cardiac rehabilitation program and remained stable later. After their cardiac event, most patients stopped smoking (Fig. 1a) and significantly reduced the grams of alcohol consumption (Table II). After 12 months, alcohol consumption increased again, though mainly with meals (Fig. 1b). Other significant changes

were also noted concerning physical activity quantified by IPAQ (Fig. 1c), hypertension drugs (Fig. 2a), treatment with metformin (Fig. 2b) and treatment with

**Table I**  
*Ergometry results before and after the cardiac rehabilitation program*

	<i>Ergometry before CRP</i>	<i>Ergometry after CRP</i>	<i>P</i>
Baseline HR (bpm)	69.2 ± 8.6	69.3 ± 11.1	0.300
Submax HR (bpm)	123.9 ± 16.9	122 ± 15.6	0.897
Baseline SBP (mmHg)	114.2 ± 18.6	112.3 ± 18.8	0.899
Submax SBP (mmHg)	148 ± 25	147.1 ± 22.4	0.896
Baseline DBP (mmHg)	71.3 ± 7.9	67.5 ± 8.8	0.357
Submax DBP (mmHg)	73 ± 9.5	71.4 ± 9.5	0.205
Time (min)	6.1 ± 2.3	7.3 ± 3	0.006
METs	7.4 ± 2.3	8.2 ± 2.8	0.045
Börg	11.7 ± 1.5	13.6 ± 1.3	<0.001

Notes to Table : Data expressed as means ± SD. CRP: cardiac rehabilitation program; Submax HR: submaximum heart rate; bpm: beats per minute; Submax SBP: submaximum systolic blood pressure; mmHg: millimetres of mercury; min: minutes; METs: metabolic equivalents.

statins (Fig. 2c) between the initial state and the visits after the acute cardiac event.

The analytical variables pre and post exercise at the beginning, at the end, and 12 months after the cardiac rehabilitation program are shown in table III (only a pre-exercise evaluation was performed at the 12-month visit). At the end of the cardiac rehabilitation program, we observed lower levels of all the study variables except for high density lipoprotein (HDL) cholesterol, which increased, and levels of uric acid, IL-6, IL-1β, adiponectin, and leptin, which remained stable. After 12 months, levels of insulin, peptide C, total cholesterol, HDL cholesterol, triglycerides, IL-6 and leptin worsened close to baseline levels whereas glucose, glycated haemoglobin (HbA1c), low density lipoprotein (LDL) cholesterol, uric acid, C-reactive protein, IL-1β, and adiponectin remained stable. Only changes in levels of total cholesterol and LDL cholesterol reached statistical significance.

Significant correlations were found between levels of IL-6, positively with C-reactive protein, HDL cholesterol, adiponectin, total cholesterol and LDL cholesterol; and negatively with levels of glucose and HbA1c. In addition, levels of IL-1β correlated positively with levels of glucose, leptin and C-reactive protein and the consumption of alcohol in grams per day, and negatively with blood pressure figures (data not shown).

**Table II**  
*Clinical and anthropometric characteristics*

	<i>Before CRP</i>	<i>After CRP</i>	<i>12 months</i>	<i>P</i>
Weight (kg)	83.8 ± 16.6	80.7 ± 14.2	83.6 ± 18.9	0.053
BMI (kg/m <sup>2</sup> )	29.5 ± 4.9	28.5 ± 4.4	29.3 ± 5.9	0.081
WC (cm)	103.7 ± 11.4	101.2 ± 8.4	104.9 ± 13.5	0.035
Fat mass (kg)	31.4 ± 8.8	26.8 ± 6.1	30.4 ± 10.9	0.042
Lean mass (kg)	52.4 ± 7.8	53.9 ± 8.1	53.2 ± 8	0.100
Basal metabolism (Kcal)	1682.1 ± 282.2	1618.9 ± 231.4	1684.9 ± 307.5	0.329
Trichopoulou questionnaire	7.4 ± 2.6	10.8 ± 1.6	10.3 ± 2.1	<0.001
IPAQ ≥ 150 min/week (%)	73.1	96.2	88.5	0.014
SBP (mmHg)	126.7 ± 14.6	119 ± 15.6	126.6 ± 18.4	0.002
DBP (mmHg)	78 ± 10.5	74.2 ± 10.8	78.6 ± 8.1	0.091
Cigarettes per day	0.3 ± 1.2	0.5 ± 1.9	0.6 ± 2	<0.001
Grams of alcohol	10.3 ± 11.5	9.9 ± 10.3	16.5 ± 12.2	<0.001
Insulin units/kg	0.01 ± 0.01	0.1 ± 0.1	0.1 ± 0.03	0.154
Nap (%)	50	57.7	53.8	0.519
Stroke (%)	0	0	7.7	0.480
PVD (%)	3.8	7.7	3.8	0.392

Notes to Table 2: Data expressed as means ± SD and %. CRP: cardiac rehabilitation program; BMI: body mass index; WC: waist circumference; SBP: systolic blood pressure; DBP: diastolic blood pressure; IPAQ: International Physical Activity Questionnaire; PVD: peripheral vascular disease.

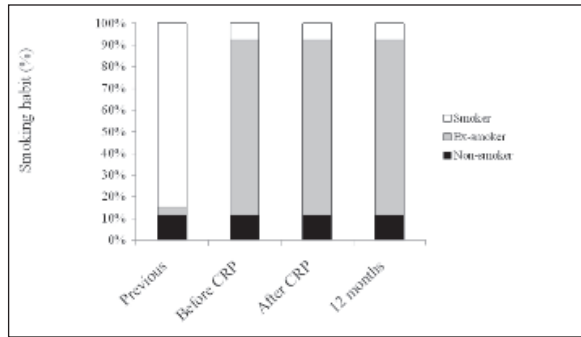


Fig. 1a: Prevalence of smoking habit.

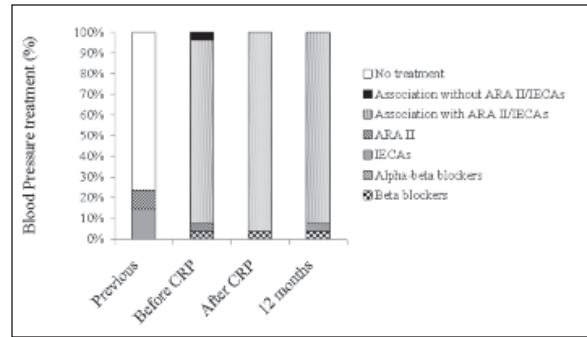


Fig. 2a: Prevalence of different blood pressure treatments.

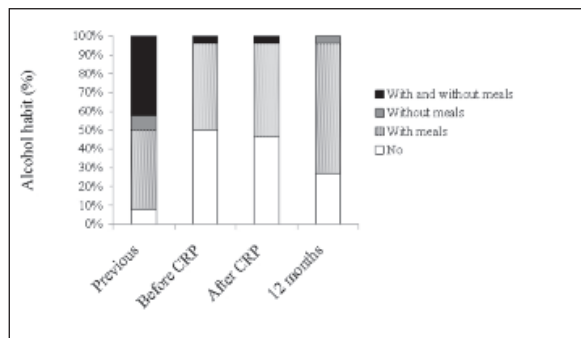


Fig. 1b: Prevalence of alcohol habit.

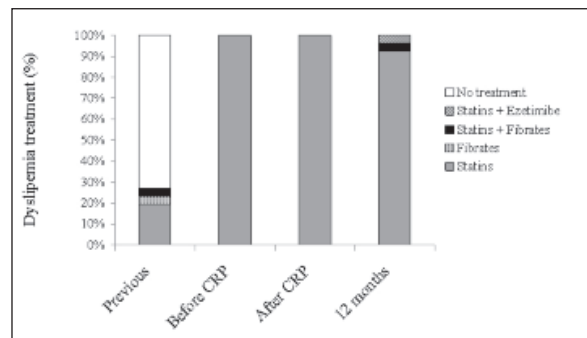


Fig. 2b: Prevalence of different dyslipidemia treatments.

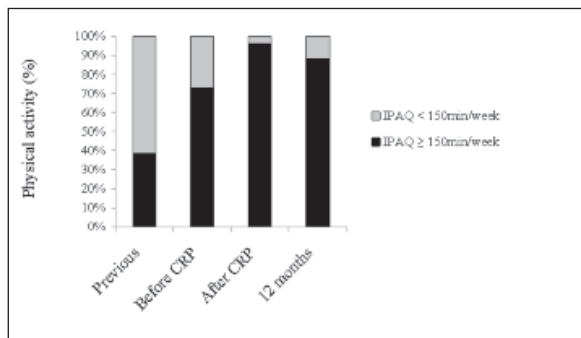


Fig. 1c: Prevalence of physical activity based on the IPAQ questionnaire.

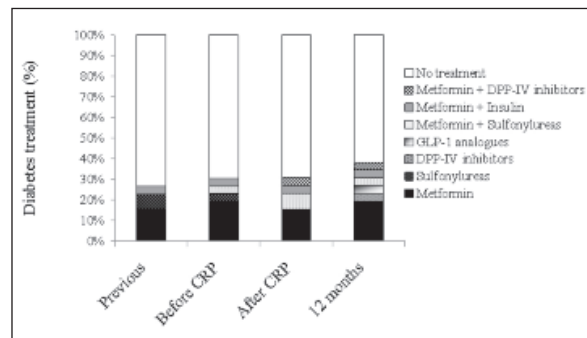


Fig. 2c: Prevalence of different diabetes treatments

Fig. 1.—Toxic habits and physical activity questionnaire.

Fig. 2.—Blood pressure, dyslipidemia and diabetes treatments.

The possible relationships between changes in body composition and changes in levels of IL-6 and IL-1 $\beta$  after the cardiac rehabilitation program were analyzed. No significant correlations were found for weight, WC or fat mass. Notably, we found a significant negative correlation between the change in levels of IL-1 $\beta$  prior to exercise and the change in METs ( $r = -0.600$ ;  $p = 0.03$ ) and a significant positive correlation between the change in levels of IL-6 prior to exercise and the change in levels of C-reactive protein ( $r = 0.604$ ;  $p = 0.01$ ), before and after the cardiac rehabilitation program.

## Discussion

Short-term studies have shown that cardiac rehabilitation programs improve the clinical, metabolic and inflammatory profile of patients with CVD and lead to a reduction in cardiac and overall mortality<sup>14,15</sup>. Our results concerning smoking cessation agree with those already published<sup>16</sup>. However, we have found no relevant data about alcohol consumption with which to compare our results. We found that the anthropometric variables and blood pressure figures decreased at the end of the cardiac rehabilitation program but increased



**Table III**  
Pre-exercise and post-exercise analytical variables before the CRP, after the CRP and 12 months later

	Before CRP pre-exercise	Before CRP post-exercise	After CRP pre-exercise	After CRP post-exercise	12 months
Glucose; mg/dl (mmol/L)	116.3 ± 28.8 (6.4 ± 1.6)	122.2 ± 23.9 (6.7 ± 1.3)	113.5 ± 15.1 (6.3 ± 0.8)	124.6 ± 45.2 (6.9 ± 2.5)	112.0 ± 19 (6.2 ± 1.1)
HbA1c; % (mmol/mol)	6.4 ± 0.7 (41.9 ± 4.6)	-	6.1 ± 0.6 (39.9 ± 3.9)	-	6 ± 0.7 (39.3 ± 4.6)
Insulin; mcU/ml (pmol/L)	14.6 ± 11.8 (104.8 ± 84.7)	49.9 ± 26.7 (358 ± 191.6) <sup>a</sup>	11.9 ± 8 (85.4 ± 57.4)	25.9 ± 19.4 (185.8 ± 139.2) <sup>b</sup>	16.1 ± 15.2 (115.5 ± 109.1)
Peptide C; ng/ml (=mcg/L)	3.2 ± 1.4	-	3.1 ± 1.1	-	3.8 ± 2.3
Total chol; mg/dl (mmol/L)	172.8 ± 34.5 (4.5 ± 0.9)	138.2 ± 26.9 (3.6 ± 0.7)	155.9 ± 30.8 (4 ± 0.8)	133.2 ± 38.2 (3.5 ± 1) <sup>b</sup>	158.2 ± 34.3 (4.1 ± 0.9) <sup>c</sup>
HDL chol; mg/dl (mmol/L)	40.3 ± 10.4 (1 ± 0.3)	47.2 ± 10.9 (1.2 ± 0.3)	42.9 ± 11.2 (1.1 ± 0.3)	44.3 ± 12.2 (1.2 ± 0.3)	40.7 ± 10.9 (1.1 ± 0.3)
LDL chol; mg/dl (mmol/L)	101.7 ± 24.1 (2.6 ± 0.6)	80 ± 17.2 (2.1 ± 0.4)	87.5 ± 22.1 (2.3 ± 0.6)	78.1 ± 16.5 (2 ± 0.4) <sup>b</sup>	88.8 ± 29.9 (2.3 ± 0.8) <sup>c</sup>
TG; mg/dl (mmol/L)	166.5 ± 73.5 (1.9 ± 0.8)	122 ± 44.1 (1.4 ± 0.5)	162.2 ± 91.5 (1.8 ± 1)	141.1 ± 79.7 (1.6 ± 0.9)	167.8 ± 115.6 (1.9 ± 1.3)
Uric acid; mg/dl (mmol/L)	6 ± 1.1 (0.4 ± 0.1)	-	5.9 ± 1.7 (0.4 ± 0.1)	-	6.1 ± 1.3 (0.4 ± 0.1)
C-reactive protein; mg/L (= mcg/ml)	10.7 ± 20.6	3.2 ± 0.3	4.5 ± 4.4	3.5 ± 1.3	4.7 ± 3.7
IL-6; pg/ml	4.3 ± 2.9	4.7 ± 2.1	4.2 ± 2.4	4.4 ± 1.7	4.9 ± 3.7
IL-1B; pg/mL	0.3 ± 0.2	0.2 ± 0.03 <sup>a</sup>	0.3 ± 0.4	0.4 ± 0.3 <sup>b</sup>	0.2 ± 0.02
Adiponectin; ng/ml	5.8 ± 3.9	-	5.7 ± 3.5	-	6.2 ± 3.7
Leptin; pg/ml	14.8 ± 13.1	-	14.4 ± 12.8	-	20.5 ± 27.8

Notes to Table 3: Data expressed as means ± SD and %. CRP: cardiac rehabilitation program; HbA1c: glycated hemoglobin; Total chol: total cholesterol; LDL chol: low density lipoprotein cholesterol; HDL chol: high density lipoprotein cholesterol; TG: triglycerides; IL-6: interleukin 6; IL-1β: Interleukin 1β.

<sup>a</sup>Significant differences between preexercise and postexercise times before CRP (p<0.05).

<sup>b</sup>Significant differences between preexercise and postexercise times after CRP (p<0.05).

<sup>c</sup>Significant differences between preexercise before CRP, after CRP and 12 months later (p<0.05).

almost back to baseline levels 12 months later, against López Frías et al.<sup>15</sup> whose patients kept the achieved positive changes in body composition after 12 months. Even if our results were modest, though still in agreement with previous data<sup>17</sup>. No significant changes were observed in carbohydrate metabolism, unlike the results described by Singh et al.<sup>18</sup> in a 3-year randomized controlled study based on moderate exercise and diet with a high quantity of fruit and vegetables. A significant decrease was found in levels of total cholesterol and LDL cholesterol in our study, though this may have been as a result of treatment with statins. Similar results were described by Brochu et al.<sup>12</sup> and Schuler et al.<sup>19</sup> after diet and exercise programs, though both studies also found improved levels of triglycerides.

Cytokine changes related to exercise are less well studied. Over recent years some authors have studied regular exercise as a natural anti-atherogenic activity and its effects on oxidative stress and inflammatory

pathways<sup>3</sup>. Our results showed that levels of C-reactive protein decreased, though not significantly, following the 2-month cardiac rehabilitation program and remained stable 12 months later. Other studies, too, have shown that aerobic exercise training induces a reduction in levels of C-reactive protein<sup>20</sup>.

At present, the role of IL-6 as a pro-inflammatory or anti-inflammatory cytokine is controversial. The release of IL-6 during exercise induces inhibition of TNF-α production and a release of other anti-inflammatory cytokines such as the IL-1 receptor antagonist and IL-10<sup>3</sup>. The patients in our study showed no significantly higher levels of IL-6 after acute exercise, in line with studies in mice<sup>21</sup> and in humans<sup>9</sup>.

Concerning CVD patients, Pereira et al.<sup>22</sup> compared the response of IL-6 after two submaximal intensities of exercise in individuals with heart failure and found no differences after low intensity and a significant increase after moderate intensity. After our cardiac

rehabilitation program there was a non-significant reduction in levels of pre-exercise IL-6. Results, though, are controversial. On one hand, some authors have found that pre-exercise levels of IL-6 decreased after different exercise programs in patients with heart failure<sup>23,24</sup>. On the other hand, others observed no changes in pre-exercise levels of IL-6 after 12 months of follow-up<sup>25</sup>, similar to our results.

Regarding the type of exercise, an eccentric exercise program in pre and postmenopausal women increased levels of IL-6 72h post-exercise<sup>26</sup>. No changes were observed after 6 weeks of moderate or high intensity resistance training in healthy young men<sup>23</sup> or after 16 weeks of moderate to high intensity resistance and concurrent training in middle-aged men<sup>27</sup>. The various exercise programs in the different studies lasted between 6 and 16 weeks.

These results are important because a significant inverse relationship has been described between physical capacity and IL-6 in patients with stable CVD<sup>28</sup>. We found significant correlations between IL-6 and certain variables. Notable among these was the positive correlation between pre-exercise IL-6 and post-exercise C-reactive protein levels at baseline. This is in agreement with Naghii et al.<sup>29</sup> who examined the effects of regular physical activity on non-lipid cardiovascular risk factors in healthy military recruits. We found a negative correlation between IL-6 and pre and post-exercise glucose levels at baseline, unlike Mitchell et al.<sup>30</sup>, who concluded that a resistance and aerobic exercise in young obese men did not influence glucose tolerance as evaluated by an oral glucose tolerance test. We also observed significant correlations in levels of IL-6 with lipid fractions, though no relevant published data were found. Hamer et al.<sup>31</sup> described a significant positive correlation between IL-6 and systolic blood pressure after acute exercise, though we did not observe this significant correlation. Unlike our results, Karch et al.<sup>32</sup> found that IL-6 levels correlated negatively with the IPAQ score.

IL-1 $\beta$  has emerged as a new inflammatory chemokine related to the metabolic syndrome. Previous studies have described a significant increase in levels of IL-1 $\beta$  in intestinal lymphocytes in mice after acute exercise<sup>17</sup>. In other study, IL-1 $\beta$  was measured at baseline, and at 3 and 6 months in Korean women with metabolic syndrome enrolled in an exercise and diet program, with no significant changes<sup>11</sup>, similar to our results. We observed significant correlations of IL-1 $\beta$ , positive with levels of C-reactive protein and negative with blood pressure figures. To our knowledge, no similar data have been published.

Assessing changes in body composition and changes in levels of IL-6 and IL-1 $\beta$  after the cardiac rehabilitation program showed no significant correlations concerning weight, WC or fat mass. Some ergometry data showed significant correlations with changes in levels of IL-6 and IL-1 $\beta$  before and after the program. As far as we are aware, no similar data have been published either.

Regarding other cytokines, some authors have found a decrease in plasma levels of adiponectin<sup>19</sup> and leptin<sup>20</sup> after acute exercise, but these data were not available in our study.

We recognize several limitations in our study. As only a few heterogeneous studies have evaluated the effects of exercise on inflammation markers in patients with CVD comparison of results is difficult, especially regarding IL-1 $\beta$ . Our patient population sample was small and our follow-up period was short if we consider the long natural history of CVD and the heterogeneity of the intervention programs published. In addition, after 12 months, patients were only evaluated pre-exercise because the gym and patient monitoring facilities were not available during and after exercise.

## Conclusion

Our patients experienced a decrease in anthropometric variables and blood pressure figures, and an improvement in lipid metabolism as a result of the cardiac rehabilitation program. However, 12 months later these variables had increased close to baseline values. Although data fail to agree, a systematic review<sup>33</sup> and a meta-analysis<sup>34</sup> conducted in patients with CVD concluded that exercise training reduced levels of IL-6. Thus, IL-6 could explain the anti-inflammatory effect of regular exercise in patients with CVD. However, our study found no significant changes in levels of IL-6 or IL-1 $\beta$  and a non-significant decline in levels of C-reactive protein after the cardiac rehabilitation program. In addition, no association was found between changes in levels of IL-6 or IL-1 $\beta$  and weight, WC or fat mass. Hence and in accordance with the recent results of the Look AHEAD study<sup>7</sup>, the absence of significant changes regarding the inflammatory status after a cardiac rehabilitation program could explain the lack of improvement in cardiovascular morbidity or mortality observed in that study, although not all of the patients were diabetic and all of them already had CVD. Further research will be needed to elucidate the effects of exercise and diet on inflammatory pathways.

## Conflict of interest

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

## Funding

L. Garrido-Sánchez is supported by a fellowship from the Fondo de Investigación Sanitaria (FIS) "Miguel Servet I" CP 13/00188.

## Acknowledgements

The authors wish to thank all the patients and IMA-BIS. We also gratefully acknowledge Ian Johnstone for his contribution to the English version of this manuscript.

## References

1. Ruiz-Cabello Turmo P, García-Molina VA, Fernández Martínez MM, Moratalla Cecilia N, Gregorio Arenas E, Aranda Ramírez P. Los países mediterráneos ante la Dieta Mediterránea, ¿Seguimos en el buen camino? El ejemplo de las mujeres de mediana edad del sur de España. *Nutr Hosp.* 2015;31(6).
2. Bonfanti N, Marcelo Fernández J, Gomez-Delgado F, Pérez-Jiménez F. Efecto de dos dietas hipocalóricas y su combinación con ejercicio físico sobre la tasa metabólica basal y la composición corporal. *Nutr Hosp.* 2014;29(3):635-43
3. Szostak J, Laurant P. The forgotten face of regular physical exercise: a 'natural' anti-atherogenic activity. *Clin Sci* 2011; 121:91-106.
4. Allen TL, Whitham M, Febbraio MA. IL-6 muscles in on the gut and pancreas to enhance insulin secretion. *Cell Metab* 2012; 15:8-9.
5. Ramírez-Vélez R, Meneses-Echavez JF, González-Ruiz K, Correa JE. Fitness muscular y riesgo cardio-metabólico en adultos jóvenes colombianos. *Nutr Hosp.* 2014;30:769-75.
6. Demarco VG, Johnson MS, Whaley-Connell AT, Sowers JR. Cytokine abnormalities in the etiology of the cardiometabolic syndrome. *Current Hypertension Reports* 2010; 12:93-8.
7. Look AHEAD Research Group, Wing RR, Bolin P, Brancati FL, Bray GA, Clark JM, Coday M, et al. Cardiovascular Effects of Intensive Lifestyle Intervention in Type 2 Diabetes. *N Engl J Med* 2013; 369:145-54.
8. Plomgaard P, Halban PA, Bouzakri K. Bimodal impact of skeletal muscle on pancreatic  $\beta$ -cell function in health and disease. *Diabetes Obes Metab* 2012; 14:78-84.
9. Ellingsgaard H, Hauselmann I, Schuler B, Habib AM, Baggio LL, Meier DT, et al. Interleukin-6 enhances insulin secretion by increasing glucagon-like peptide-1 secretion from L cells and alpha cells. *Nat Med* 2011; 17:1481-9.
10. Reihmane D, Jurka A, Tretjakovs P. The relationship between maximal exercise-induced increases in serum IL-6, MPO and MMP-9 concentrations. *Scand J Immunol* 2012; 76:188-92.
11. Eui Geum Oh, So Youn Bang, Soo Hyun Kim, Sa Saeng Hyun, Sang Hui Chu, Justin YJ, et al. Therapeutic Lifestyle Modification Program Reduces Plasma Levels of the Chemokines CRP and MCP-1 in Subjects With Metabolic Syndrome. *Biological Research for Nursing* 2013; 15:48-55.
12. Guidelines for Data Processing and Analysis of the International Physical Activity Questionnaire (IPAQ) – Short and Long Forms. November 2005; [www.ipaq.ki.se/scoring.pdf]
13. Trichopoulos A, Costacou T, Bamia C, Trichopoulos D. Adherence to a Mediterranean diet and survival in a Greek population. *N Engl J Med* 2003; 348: 2599-608.
14. Taylor RS, Brown A, Ebrahim S, Jolliffe J, Noorani H, Rees K, et al. Exercise-based rehabilitation for patients with coronary heart disease: systematic review and meta-analysis of randomized controlled trials. *Am J Med* 2004; 116:682-92.
15. López Frías M, Gómez Martínez M, Ramírez López Frías M, De Teresa Galván C, Díaz Castro J, Nestares T. Beneficio del seguimiento de un programa de rehabilitación cardíaca sobre algunos parámetros de la composición corporal. *Nutr Hosp.* 2014;30(6):1366-74.
16. A Chatziefstratiou A, Giakoumidakis K, Brokalaki H. Cardiac rehabilitation outcomes: modifiable risk factors. *Br J Nurs.* 2013; 22:200-7.
17. Savage PD, Brochu M, Poehlman ET, Ades PA. Reduction in obesity and coronary risk factors after high caloric exercise training in overweight coronary patients. *Am Heart J* 2003; 146:317-23.
18. Singh RB, Rastogi V, Rastogi SS, Niaz MA, Beegom R. Effect of diet and moderate exercise on central obesity and associated disturbances, myocardial infarction and mortality in patients with and without coronary artery disease. *J Am Coll Nutr* 1996; 15:592-601.
19. Schuler G, Hambrecht R, Schlierf G, Niebauer J, Hauer K, Neumann J, et al. Regular physical exercise and low-fat diet. Effects on progression of coronary artery disease. *Circulation* 1992; 86:1-11.
20. Stavropoulos-Kalinoglou A, Metsios GS, Veldhuijzen van Zanten JJ, Nightingale P, Kitas GD, Koutedakis Y. Individualised aerobic and resistance exercise training improves cardiorespiratory fitness and reduces cardiovascular risk in patients with rheumatoid arthritis. *Ann Rheum Dis.* 2013; 72:1819-25.
21. Pervaiz N, Hoffman-Goetz L. Immune cell inflammatory cytokine responses differ between central and systemic compartments in response to acute exercise in mice. *Exerc Immunol Rev* 2012; 18:142-57.
22. Pereira DA, Ribeiro-Samora GA, Vieira DS, Pereira LS, Coelho FM, Parreira VF, et al. Evaluation of the inflammatory response to two different intensities of exercise in individuals with heart failure. *Inflammation* 2012; 35:509-15.
23. Pil-Byung C, Shin-Hwan Y, Il-Gyu K, Gwang-Suk H, Jae-Hyun Y, Han-Joon L, et al. Effects of exercise program on appetite-regulating hormones, inflammatory mediators, lipid profiles, and body composition in healthy men. *J Sports Med Phys Fitness* 2011; 51:654-63.
24. Fu TC, Wang CH, Lin PS, Hsu CC, Cherng WJ, Huang SC, et al. Aerobic interval training improves oxygen uptake efficiency by enhancing cerebral and muscular hemodynamics in patients with heart failure. *Int J Cardiol* 2013; 167:41-50.
25. Lindgärde F, Gottsäter A, Åhrén B. Positive correlation between tumor necrosis factor (TNF)- $\alpha$  and cardiorespiratory fitness after six-months of regular aerobic exercise in Peruvian Amerindian women. *Rev Med Chil* 2011; 139:998-1005.
26. Conceição MS, Libardi CA, Nogueira FR, Bonganha V, Gáspari AF, Chacon-Mikahil MP, et al. Effects of eccentric exercise on systemic concentrations of pro- and anti-inflammatory cytokines and prostaglandin (E<sub>2</sub>): comparison between young and postmenopausal women. *Eur J Appl Physiol* 2012; 112:3205-13.
27. Libardi CA, De Souza GV, Cavaglieri CR, Madruga VA, Chacon-Mikahil MP. Effect of resistance, endurance, and concurrent training on TNF- $\alpha$ , IL-6, and CRP. *Med Sci Sports Exerc* 2012; 44:50-6.
28. Byrkjeland R, Nilsson BB, Westheim AS, Arnesen H, Seljeflot I. Inflammatory markers as related to disease severity in patients with chronic heart failure: limited effects of exercise training. *Scand J Clin Lab Invest* 2011; 71:598-605.
29. Naghii MR, Aref MA, Almadadi M, Hedayati M. Effect of regular physical activity on non-lipid (novel) cardiovascular risk factors. *Int J Occup Med Environ Health* 2011; 24:380-90.
30. Mitchell JB, Phillips MD, Yellott RC, Currie LM. Resistance and aerobic exercise: the influence of mode on the relationship between IL-6 and glucose tolerance in young men who are obese. *J Strength Cond Res* 2011; 25:1529-37.
31. Hamer M, Steptoe A. Vascular inflammation and blood pressure response to acute exercise. *Eur J Appl Physiol* 2012; 112:2375-9.
32. Karch I, Olszowska M, Tomkiewicz Pająk L, Drapisz S, Luszczak J, Podolec P. The effect of physical activity on serum levels of selected biomarkers of atherosclerosis. *Kardiol Pol* 2013; 71:55-60.
33. Smart NA, Steele M. The effect of physical training on systemic proinflammatory cytokine expression in heart failure patients: a systematic review. *Congest Heart Fail* 2011; 17:110-4.
34. Swardfager W, Herrmann N, Cornish S, Mazereeuw G, Marzolini S, Sham L, et al. Exercise intervention and inflammatory markers in coronary artery disease: a meta-analysis. *Am Heart J* 2012; 163:666-76.