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Reduction in C-Reactive Protein Through Cardiac Rehabilitation and Exercise Training

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OBJECTIVES This study was designed to assess the effects of three-month formal phase II cardiac rehabilitation and exercise training programs on high-sensitivity C-reactive protein (HSCRP) levels in patients with coronary heart disease (CHD).

BACKGROUND High-sensitivity C-reactive protein is associated with abdominal adiposity and other CHD risk factors and is a potent independent predictor of CHD events. Although weight reduction and statin therapy reduce HSCRP levels, the independent effects of cardiac rehabilitation programs on HSCRP are not well established.

METHODS We analyzed plasma levels of HSCRP in 277 patients with CHD (235 consecutive patients before and after formal phase II cardiac rehabilitation and exercise training programs and 42 "control" patients who did not attend cardiac rehabilitation). Additionally, we determined the effects of cardiac rehabilitation on HSCRP independent of statin therapy and weight loss.

RESULTS Rehabilitation patients improved significantly in body fat, obesity indices, exercise capacity, and other cardiac risk factors. Mean (5.9 ± 7.7 to 3.8 ± 5.8 mg/l; -36%; $p < 0.0001$) and median levels of HSCRP (-41%; $p = 0.002$) decreased significantly in the rehabilitation group but not in the control population. Similar significant reductions in HSCRP occurred in the rehabilitation patients regardless of whether they received statin therapy or lost weight.

CONCLUSIONS Therapeutic lifestyle changes effected through a three-month cardiac rehabilitation program significantly improved numerous cardiac risk factors. Through this holistic approach to secondary prevention, we observed significant reductions in HSCRP levels. These findings identify another clinical modality of reducing HSCRP beyond use of statin drugs and suggest an additional benefit of formal phase II cardiac rehabilitation and exercise training programs. (J Am Coll Cardiol 2004;43:1056–61) © 2004 by the American College of Cardiology Foundation

Atherothrombosis is recognized as a dynamic chronic inflammatory process of the vessel wall in which phases of inflammatory and thrombotic activity underlie the clinical presentation of acute coronary syndromes (ACS) (1,2). Research has suggested that inflammatory markers, such as high-sensitivity C-reactive protein (HSCRP), provide an alternative method for global assessment of cardiovascular risk (3–5). Several prospective studies have shown that plasma levels of HSCRP are a strong independent predictor of risk of future vascular events among individuals with and without known cardiovascular disease, including those patients who have been recently discharged from an ACS (5–12).

Elevated levels of HSCRP have been positively correlated with most cardiovascular risk factors, and have a strong association with adiposity and to a lesser extent physical inactivity (13–17). We have recently demonstrated the strong association between metabolic syndrome and elevated levels of HSCRP in our coronary heart disease (CHD) population (18). At the present time, proven therapies to reduce high-risk HSCRP levels include weight reduction (19) and, particularly, statin therapy (11,20–22).

Although cardiac rehabilitation and exercise training is a proven modality for reducing the overall burden of cardiovascular risk, and can be effective in reducing body fat and enhancing exercise capacity in patients following major cardiac events (23–26), the effects of this therapy on HSCRP are not well established. However, we have recently reported marked reductions in levels of HSCRP in our patients with metabolic syndrome following cardiac rehabilitation (18).

In the present study, we sought to determine the effects of a vigorous nonpharmacologic program of formal phase II cardiac rehabilitation and exercise training on levels of HSCRP in patients following major cardiac events and to determine if this therapy reduces HSCRP independent of statin therapy and weight loss.

METHODS

We reviewed the case records of 235 consecutive patients with CHD (72% percutaneous intervention [PCI], 19% bypass surgery, and 28% myocardial infarction) completing a three-month formal program of cardiac rehabilitation and exercise training to ascertain relevant anthropometric, lipid, and clinical data. This study was approved by the Institutional Review Board at Ochsner Clinic Foundation. Detailed program components have been reviewed elsewhere (23–26), but in brief, patients received both individual and group counseling from a registered dietitian in dietary management as recommended by the Adult Treatment Panel III guidelines, as well as special emphasis on the Mediterranean diet (27,28). In overweight

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Abbreviations and Acronyms

ACS = acute coronary syndromes
BMI = body mass index
CHD = coronary heart disease
HSCRP = high-sensitivity C-reactive protein
PCI = percutaneous coronary intervention
VO_2 = oxygen consumption

patients, modifications in the diet plan were introduced in order to promote weight loss. Patients received formalized exercise instruction and met three times per week for group exercise classes, and were encouraged to exercise on their own (1 to 3 times per week) in between sessions. Although compliance with formal rehabilitation and exercise sessions was assessed, we did not record compliance with home exercise frequency or duration. Patients' exercise recommendations were tailored towards the anaerobic threshold achieved during entry testing. Specific weight management guidance was given to those overweight and obese subjects. Educational classes were given with regards to all aspects of CHD risk including hypertension, smoking cessation, and diabetes management.

A group of 42 subjects who entered rehabilitation during the same time period, but dropped out before beginning active participation in the program, agreed to serve as a control group for the purpose of monitoring HSCRP, lipids, and body mass index (BMI) over time; these patients, however, did not have cardiopulmonary exercise tests. All subjects underwent initial evaluation including HSCRP assessment two to six weeks following hospital discharge, and repeat measurements of these parameters were performed between three and six months following initial testing. The principal reasons for not participating in the program were financial (55%) and traveling distance to the rehabilitation facility (33%). The diagnoses of control subjects included 79% following PCI, 21% after coronary bypass, and 24% with myocardial infarction.

In all rehabilitation patients, fasting lipids, glucose, HSCRP, percent body fat, abdominal girth, and resting blood pressure were obtained on the same day prospectively upon entry and completion of the formal rehabilitation program. The majority of subjects entered the program between three and five weeks following hospital discharge. High-sensitivity assays for CRP were performed according to methods described by the manufacturer (Dade Behring Inc., Deerfield, Illinois) (29). The percentage of body fat was determined by the skinfold technique using the average of three skinfolds (thigh, chest, and abdomen in men; thigh, triceps, and suprailium in women) (30,31). All measurements were made in the early morning before exercise.

Patients and control subjects who were taking either lipid-lowering medication (65% of rehabilitation patients, 60% of control subjects), including statins, or hormone replacement therapy remained on constant doses for a period of at least six weeks before the initial assessment and throughout the evaluation period.

Table 1. Baseline Differences Between Rehabilitation and Control Subjects

	Rehabilitation (n = 235)	Control (n = 42)	p Value
Age (yrs)	66.7 ± 11	63.9 ± 11.1	0.05
% Women	29%	17%	0.01
Total cholesterol (mg/dl)	173 ± 37	181 ± 35	NS
HDL-C (mg/dl)	42 ± 14	44 ± 18	NS
LDL-C (mg/dl)	103 ± 41	107 ± 47	NS
Triglycerides (mg/dl)	152 ± 89	169 ± 93	NS
Glucose (mg/dl)	105 ± 23	109 ± 27	NS
Mean HSCRP (mg/l)	5.9 ± 7.7	6.3 ± 6.9	NS
Median HSCRP (mg/l)	3.4	3.6	NS
Weight (lbs)	183 ± 35	189 ± 33	NS
BMI (kg/m^2)	27.9 ± 4.9	29.2 ± 5.0	NS
% Overweight	38%	41%	NS
% Obese	31%	33%	NS
% Lipid-lowering meds	65%	60%	NS
% Statin use	61%	55%	NS

BMI = body mass index; HDL-C = high-density lipoprotein cholesterol; HSCRP = high sensitivity C-reactive protein; LDL-C = low-density lipoprotein cholesterol; NS = not specified.

Means or proportions for baseline risk factors were computed for all subjects, and the significance of any differences in means tested with the Student *t* test; differences in proportions were tested with the chi-square statistic. Because the distributions of CRP are rightward skewed, median concentrations were computed for this parameter and the significance of any differences assessed using the Wilcoxon rank-sum test. Statistical analysis using paired and unpaired *t* test was performed using Statview 5.0.1 (SAS Institute, Cary, North Carolina). A value of $p \leq 0.05$ was considered statistically significant, and variability is reported using standard deviation.

RESULTS

Baseline data on the 235 patients enrolled in the rehabilitation program are detailed in Table 1. In our rehabilitation cohort, 67 (29%) patients were women (33% on hormone replacement therapy), and the mean age of our cohort was 66 ± 11 years. Baseline assessment (including HSCRP) was obtained 29 ± 10 days in rehabilitation patients and 32 ± 12 days in control patients following the cardiac event (p = NS between groups). The mean BMI of the cohort was 27.9 ± 4.9 kg/m^2, and the mean percentage of body fat was 28.7% ± 7.8%. Of note, 38% of subjects upon entry were classified as overweight (BMI ≥25 kg/m^2 and <30 kg/m^2), and an additional 31% were classified as obese (BMI ≥30 kg/m^2). The median concentration of HSCRP at entry was 3.4 mg/l (range 0.2 to 48.2 mg/l); mean concentration was 5.9 ± 7.7 mg/l at baseline. 143 patients (61%) were on statin therapy upon entry and during the three-month rehabilitation program. An additional 10 patients (4%) were on either fibrate or niacin therapy. At entry, HSCRP was weakly, but significantly, correlated to BMI (r = 0.114; p = 0.05), but did not correlate with other baseline factors, including peak exercise capacity.

Table 1 also highlights the baseline differences between the

Table 2. Effects of Cardiac Rehabilitation and Exercise Training (n = 235)

	Before	After	% Change	p Value
Total cholesterol (mg/dl)	172 ± 38	174 ± 36		NS
HDL-C (mg/dl)	41.6 ± 13.6	44.4 ± 13.7	7%	<0.0001
LDL-C (mg/dl)	103 ± 41	104 ± 39		NS
Triglycerides (mg/dl)	152 ± 89	141 ± 80	−7%	0.05
Glucose (mg/dl)	105 ± 23	105 ± 24		NS
Median HSCRP (mg/l)	3.4	2.0	−41%	0.002
Mean HSCRP (mg/l)	5.9 ± 7.7	3.8 ± 5.8	−36%	<0.0001
Anaerobic threshold (ml/kg/min)	11.7 ± 3.0	11.9 ± 3.7	2%	0.04
Peak VO_2 (ml/kg/min)	16.6 ± 5.1	18.1 ± 5.9	9%	<0.0001
Abdominal girth (inches)	39.8 ± 5.0	38.9 ± 5.1	−2%	0.002
BMI (kg/m^2)	27.9 ± 4.9	27.8 ± 4.7		NS
Percent fat	28.7 ± 7.8	27.7 ± 7.2	−3%	0.0008
% Overweight	38%	49%		0.01
% Obese	31%	26%		0.002

VO_2 = oxygen consumption; other abbreviations as in Table 1.

control and rehabilitation subjects. Of the control subjects, 7 (17%) were women (29% on hormone replacement therapy), which was significantly lower than the rehabilitation population. The control patients were also slightly younger (63.9 ± 11.1 years vs. 66.7 ± 11.2 years; p = 0.05). There were no differences in lipids, use of lipid medications, BMI, or HSCRP levels between the two groups.

Follow-up assessment (including HSCRP) was obtained on the day of program completion, which averaged 134 ± 25 days in rehabilitation patients and 139 ± 27 days in control patients following the cardiac event (p = NS between groups). Table 2 describes the effects of cardiac rehabilitation and exercise training on various parameters of risk. Significant improvements occurred in most parameters of cardiovascular risk including high-density lipoprotein cholesterol, triglycerides, exercise capacity (anaerobic threshold and peak oxygen consumption [VO_2]), and body fat. The percent of subjects identified as obese (BMI ≥30 kg/m^2) was reduced from 31% upon entry to 26% upon completion of the rehabilitation program. This resulted in an increase of patients classified as overweight (38% to 49%).

Median values of HSCRP decreased 41% (mean reduction 36%) in patients enrolled in cardiac rehabilitation and exercise training programs, which contrasts with the lack of change in HSCRP in the control subjects (Tables 2 and 3, Fig. 1). These changes in HSCRP did not correlate with changes in any other value studied (change in weight, BMI, percent fat, or exercise capacity). In addition, control subjects demonstrated an increase in triglycerides over time and trended towards an increase in low-density lipoprotein cholesterol and weight. Elevated HSCRP levels (≥3.0 mg/l) were present in 122 patients (54%) at baseline and 86 patients (38%) upon completion of cardiac rehabilitation and exercise training. In contrast, elevated HSCRP levels were present in 57% and 52% of control subjects at baseline and follow-up respectively. The distributions of baseline and follow-up HSCRP values are outlined in Figure 2, demonstrating that values ≥6 mg/l were present in 30% of patients before rehabilitation and were reduced to only 16% following the intervention program. Moreover, values >15 mg/l were present in 9% of patients before rehabilitation and were reduced to only 1% following the intervention program.

Table 3. Changes in Lipids, HSCRP, and Body Mass in Control Subjects (n = 42)

	Baseline	Follow-Up	p Value
Total cholesterol (mg/dl)	181 ± 35	197 ± 41	NS
HDL-C (mg/dl)	44 ± 18	43 ± 19	NS
LDL-C (mg/dl)	107 ± 47	118 ± 49	0.07
Triglycerides (mg/dl)	169 ± 93	182 ± 102	0.05
Glucose (mg/dl)	109 ± 27	109 ± 25	NS
Mean HSCRP (mg/l)	6.3 ± 6.9	6.6 ± 7.0	NS
Median HSCRP (mg/l)	3.6	3.7	NS
Weight (lbs)	189 ± 33	195 ± 35	NS
BMI (kg/m^2)	29.2 ± 5.0	29.4	NS
% Overweight	41%	43%	NS
% Obese	33%	36%	NS

Abbreviations as in Table 1.

The effects of cardiac rehabilitation and exercise training on HSCRP were then assessed in patients who were actively taking statin therapy versus those patients who were statin-naive. Patients on statin therapy (n = 143) had a 42% reduction in HSCRP (3.45 to 2.0 mg/l, p = 0.002), which is similar to that observed in statin-naive patients (n = 82) (3.2 to 2.0 mg/l, −38%, p = 0.003) (Fig. 3).

We further assessed the non-anthropometric effects of cardiac rehabilitation and exercise training on median and

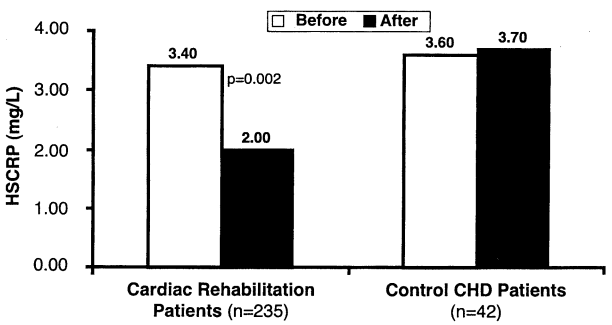

Figure 1. Median changes in high-sensitivity C-reactive protein (HSCRP) in cardiac rehabilitation and in control patients with coronary heart disease (CHD).

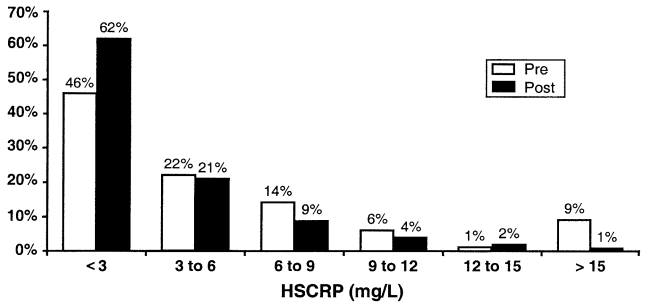

Figure 2. Distribution of high-sensitivity C-reactive protein (HSCRP) in patients with coronary artery disease (n = 235) before and after cardiac rehabilitation and exercise training.

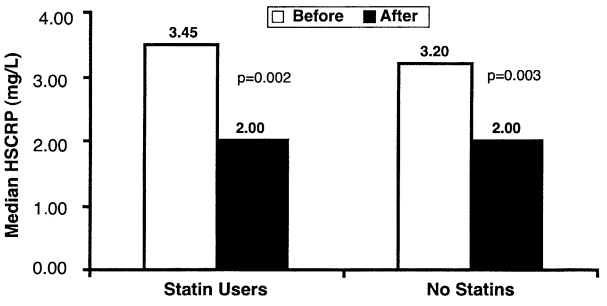

Figure 3. Change in high-sensitivity C-reactive protein (HSCRP) following cardiac rehabilitation and exercise training in patients taking statins (n = 143) and in patients not taking statins (n = 82).

mean levels of HSCRP by dividing the rehabilitation patients into those who lost weight, and comparing their changes in HSCRP to those patients who gained weight, during the three-month intervention program (Table 4). Eight patients had no change in weight; 121 patients lost weight (mean weight change −5.8 lbs, $p < 0.0001$; mean BMI change −0.9 kg/m^2, $p < 0.0001$; mean absolute percent fat change −1.8%, $p = 0.001$) and also reduced median levels of HSCRP by 44% (3.4 to 1.9 mg/l, $p = 0.003$). A total of 106 patients gained weight (mean weight change +5.7 lbs, $p < 0.0001$; mean BMI change +0.9 kg/m^2, $p < 0.0001$; mean absolute percent fat change −0.1%, p = NS) and also reduced median levels of HSCRP by 40% (3.35 to 2.0 mg/l, $p = 0.004$) (Fig. 4).

DISCUSSION

This study demonstrates that therapeutic lifestyle changes, effected through a three-month program of cardiac rehabilitation and exercise training, can produce significant improvements in numerous cardiac risk factors, including lipids, exercise capacity, and obesity parameters. To our knowledge, this is the first report of the favorable effects of this therapy on HSCRP independent of statin therapy and weight reduction.

Atherosclerosis is characterized by inflammation in the vessel wall, particularly at the site of the unstable atherosclerotic plaque (2). In the active plaque, macrophages and T-lymphocytes produce proinflammatory cytokines such as interleukin 6 and 8 and tumor necrosis factor, which increase systemic markers of inflammation such as C-reactive protein (2,14). In addition to being a marker of inflammation, CRP has recently been found to possess activity that promotes the atherothrombotic process (32–36). Large cohort studies have shown an association between elevated levels of circulating CRP and increased risk for cardiac events or death, in apparently healthy individuals, in patients with stable angina, and in patients following an ACS (5–12,37–40). We recently reported the high prevalence of metabolic syndrome in our CHD population and the markedly elevated levels of HSCRP in this population (18).

Our present study found levels of HSCRP to be elevated in patients following major cardiac events, with the majority of subjects falling in the fourth and fifth quintiles of distribution for healthy individuals. As a result of the intervention program, we observed a 41% median reduction in levels of HSCRP. This reduction was of similar or greater

Table 4. Changes in Weight, BMI, Body Fat, and HSCRP Following Cardiac Rehabilitation and Exercise Training in Patients Who Achieved Weight Loss (A) Versus Patients Who Gained Weight (B)

A. Weight Losers (n = 121)				
	Before	**After**	**% Change**	**p Value**
Weight (lbs)	187 ± 37	181 ± 35	−3%	< 0.0001
BMI (kg/m^2)	28.6 ± 5.0	27.7 ± 4.6	−3%	< 0.0001
Percent fat	30.0 ± 7.9	28.2 ± 7.6	−6%	0.0001
Median HSCRP (mg/l)	3.4	1.9	−44%	< 0.001
Mean HSCRP (mg/l)	5.9 ± 7.3	4.1 ± 6.9	−31%	0.0065
B. Weight Gainers (n = 106)				
	Before	**After**	**% Change**	**p Value**
Weight (lbs)	178 ± 33	184 ± 35	+3%	< 0.0001
BMI (kg/m^2)	27.1 ± 4.7	28.0 ± 4.9	+3%	< 0.0001
Percent fat	27.2 ± 7.5	27.1 ± 7.5	0	NS
Median HSCRP (mg/l)	3.35	2.0	−40%	< 0.001
Mean HSCRP (mg/l)	5.9 ± 8.1	3.4 ± 4.0	−42%	0.002

Abbreviations as in Table 1.

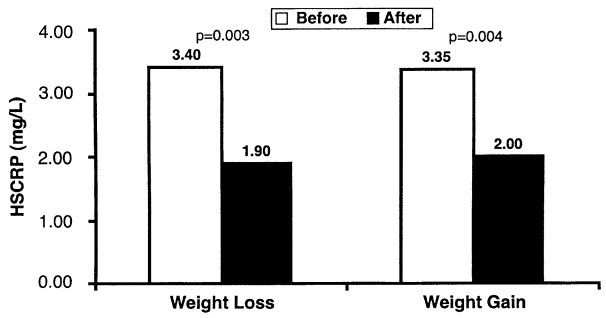

Figure 4. Changes in high-sensitivity C-reactive protein (HSCRP) following cardiac rehabilitation and exercise training in patients who achieved weight loss (n = 121) versus patients who gained weight (n = 106).

magnitude to that observed in multiple studies using statin therapy, where median reductions in HSCRP were reported to be between 15% and 20% (11,20–22). Following publication of these important observations, statins were discovered to possess immunomodulating activity, and at the present time generally remain the major treatment option available to the clinician pursuing therapy for elevated HSCRP (41), although recent evidence indicates that other lipid therapies, including niacin, ezetimibe, and possibly fibrates may also reduce HSCRP (42–44).

To assess the unique and independent effects of the nonpharmacologic program, we assessed changes in HSCRP in patients who were actively taking statin therapy. We found similar reductions in HSCRP in patients taking statins and those who were not on lipid-lowering agents (Fig. 3), suggesting that the effects of the rehabilitation program are unique and incremental over those of statin therapy. This suggests that potentially a 50% or greater reduction in HSCRP could be achieved in patients initially treated with statins coupled with an aggressive nonpharmacologic strategy such as a formal phase II program of cardiac rehabilitation and exercise training.

There was a positive relationship between adiposity and HSCRP levels across our CHD population, which has been previously described, and it is known that adipocytes synthesize cytokines that are involved in the production of CRP (13–17,45–47). Previous studies have shown that weight loss can reduce levels of CRP (19). Following nonpharmacologic intervention with cardiac rehabilitation and exercise training, we observed significant improvements in abdominal adiposity, as evidenced by reductions in mean abdominal girth and percent body fat. To assess whether other aspects of the cardiac rehabilitation program beyond those of weight reduction could have a salutary effect on levels of HSCRP, we divided our cohort into weight losers and weight gainers (Table 4, Fig. 4). We observed similar reductions in HSCRP regardless of variation in weight, suggesting that other aspects of the intervention program, including dietary modification and exercise training, may have played a prominent role in reducing inflammation. It is known that n-3 fatty acids, prominent in the Mediterranean diet promoted in our patients, possess potent anti-inflammatory effects, including inhibition of TNF and interleukin production (28,48–50). Furthermore, a recent analysis of 3,638 men participating in the National Health and Nutrition Examination Survey III found a strong and independent inverse relationship between degree of exercise and levels of CRP (51). Similarly, a small prospective controlled study of exercise training in healthy men reported a significant fall in median CRP levels following nine months of endurance exercise training (52). These data suggest that multiple components of the rehabilitation process likely contributed to the reductions in CRP we observed.

A few study limitations should be mentioned. Our study was not randomized, raising the possibility of selection bias, particularly because the control population chose not to attend the cardiac rehabilitation program. In addition, our control group was much smaller than the study cohort, and the groups differed in a few baseline characteristics (such as age and gender), but were similar in most parameters assessed. Although we instructed the intervention group in the Mediterranean diet, we did not measure dietary intake or blood levels of n-3 fatty acids to demonstrate compliance with our recommendations.

In summary, despite the study limitations described earlier, we believe our data demonstrate that formal cardiac rehabilitation and exercise training produce significant reductions in HSCRP of similar or greater magnitude as therapy with statin drugs, thus adding to the well-proven benefits of this therapy. Moreover, the effects of this therapy appear to be independent of the effects of statin therapy and weight loss on HSCRP. In addition to receiving appropriate pharmacotherapy, patients with CHD following cardiac events should be routinely referred to cardiac rehabilitation and exercise training to provide incremental cardiovascular benefits in secondary coronary prevention.

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