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C-reactive protein levels according to physical activity and body weight for participants in the coronary health improvement project

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Abstract

Objectives. To identify whether the Coronary Health Improvement Project (CHIP), an intervention designed to increase physical activity and improve diet, lowers serum C-reactive protein (CRP). The study will also assess whether changes in CRP over the study period are associated with baseline levels of and changes in selected coronary risk factors.

Methods. A randomized controlled study design assigned 348 individuals to the intervention or control group with measurements taken at baseline, 6 weeks, and 6 months of body weight, physical activity, and serum CRP levels. Participants attended an intensive 40-hour educational course delivered over a 4-week period, beginning March 2003, in Rockford, IL, USA.

Results. The intervention significantly increased physical activity and decreased BMI, weight, percent body fat, and saturated fat ($P<0.0001$). However, the intervention was not significantly associated with a decrease in CRP. Participants in both the intervention and control groups combined showed a decrease in high CRP (>3 mg/L), from 46% at baseline to 38% at 6 weeks and 41% at 6 months. Those with higher BMI at baseline showed a greater increase in CRP over time ($P<0.0001$), whereas those with higher CRP at baseline showed a greater decrease in CRP over time ($P<0.0001$).

Conclusions. Over 6 week and 6 month follow-up periods, the intervention failed to discriminate changes in CRP. However, the percentage with high CRP did fall, more so for those with lower BMI and higher CRP at baseline. BMI may mediate the influence of physical activity on CRP.

Keywords: C-reactive protein (CRP); Physical activity; Body weight; Percent body fat; Saturated fat; Body mass index (BMI); Coronary Health Improvement Project (CHIP)

Introduction

C-reactive protein (CRP) is a nonspecific acute-phase reactant that has traditionally been used to detect acute injury, infection, and inflammation (Backes et al., 2004). Some of the typical causes of inflammation are cytomegalovirus, chlamydia pneumoniae, dyslipidemia, obesity, and/or hormone replacement therapy (Sobal and Sinzinger, 2005). Studies have shown a positive independent association between CRP and atherosclerotic events (Backes et al., 2004; Kasapis and Thompson, 2005; Ledue and Rifai, 2003), future cardiovascular events in patients with acute coronary artery disease, history of myocardial infarction, and angina pectoris (Cushman et al., 2005; Ridker, 2001, 2003; Jialal and Devaraj, 2003), and other cardiovascular risk factors, such as body weight and body fat (Godefroi et al., 2005; Wu et al., 2006; Lim et al., 2006). It has also been shown that high CRP is a significant and independent risk predictor of nontraumatic bone fractures (Schett et al., 2006).

The level of serum CRP indicates the severity of inflammation (Coppola et al., 2006). Studies have determined that CRP

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levels above 3 mg/L are a good prognostic marker for future vascular events. People with and without cardiovascular arterial disease (CAD) with CRP levels above 3 mg/L are at significantly greater risk of ischemic episodes than those with CRP below 3 mg/L (Backes et al., 2004; Coppola et al., 2006). Serum CRP levels from 1 to 3 mg/L and below 1 mg/L have been shown to be at normal and low risk for CAD, respectively.

C-reactive protein levels can be lowered through drug therapy (Sobal and Sinzinger, 2005). There is also evidence that a lifestyle intervention that improves a person's physical activity and/or eating habits may reduce CRP (Caulin-Glaser et al., 2005; Blum et al., 2006). Reduction of CRP levels through physical activity and weight loss is a practical way of reducing the likelihood of a cardiac event. The Coronary Health Improvement Project (CHIP) is a specific lifestyle intervention program that may positively impact CRP levels (Diehl, 1998). It is a 4-week health education intervention program that teaches participants how to improve their eating habits and physical activity in order to benefit their cardiac health. It is assumed that the program will reduce CAD risk factors, including CRP levels.

This study will evaluate whether the CHIP program is efficacious at lowering serum CRP. It will also explore whether changes in CRP over the study period are associated with changes in selected coronary risk factors.

Methods

Subject recruitment

The SwedishAmerican Center for Complementary Medicine (SACCM) recruited participants for this study from September 2002 to March 2003. Recruitment was from the Rockford, IL metropolitan area with the requirement that participants be 18 years of age or older. All participants provided informed consent. Many enrolled with a spouse or significant other. For those who participated in the program with their partner (42%), the unit of randomization was *pairs*. For those who participated as individuals (58%), the unit of randomization was *individuals*. No significant differences were observed between pairs and individuals. Randomization was determined by a random number generator. The study coordinator conducted the participant sign-up process, randomization, and group assignments. Participants were excluded from the study if they had a significant condition or major illness that would prevent them from exercising. The process from enrollment, allocation, follow-up, to analysis is shown in Fig. 1. Three hundred forty-eight participants were identified and randomly assigned to the intervention or control group, resulting in 174 per group. The intervention and follow-up phase of the study was from March through September 2003. Through 6 months 21 people in the intervention group and 9 people in the control group were lost to follow-up. The Institutional Review Board of the SwedishAmerican Health System approved the study on August 29, 2002.

Design

The study was a randomized controlled trial involving intervention and control groups. Measurements were taken at baseline, 6 weeks, and 6 months. The health education intervention was received during the first 4 weeks. The control group received no intervention during the 6 month follow-up period and was specifically told not to alter their lifestyle during the investigative period.

The sample size for this study was powered based on anticipated intervention effects on BMI and exercise. A post hoc assessment of CRP indicates that the intervention lowered the percentage with high CRP from 48 at baseline to 40 at 6 weeks to 40 at 6 months. For a level of significance of 0.05 (one-tailed) and beta equal to 0.20 (power=0.80), the required sample size to detect a significant change was 603 per group for 6 weeks and for 6 months.

Intervention

The CHIP (Diehl, 1998) is an intensive community-based education intervention. Participants are required to attend a 4-week course. Four 2-hour classes are taught each week resulting in a total class time of approximately 32 h for the entire course. Theory-based intervention planning was used to develop the curriculum, class design, alumni association, and take-home assignments (Lupton et al., 2003; Tudor-Locke et al., 2004; Toobert et al., 2003). The intervention

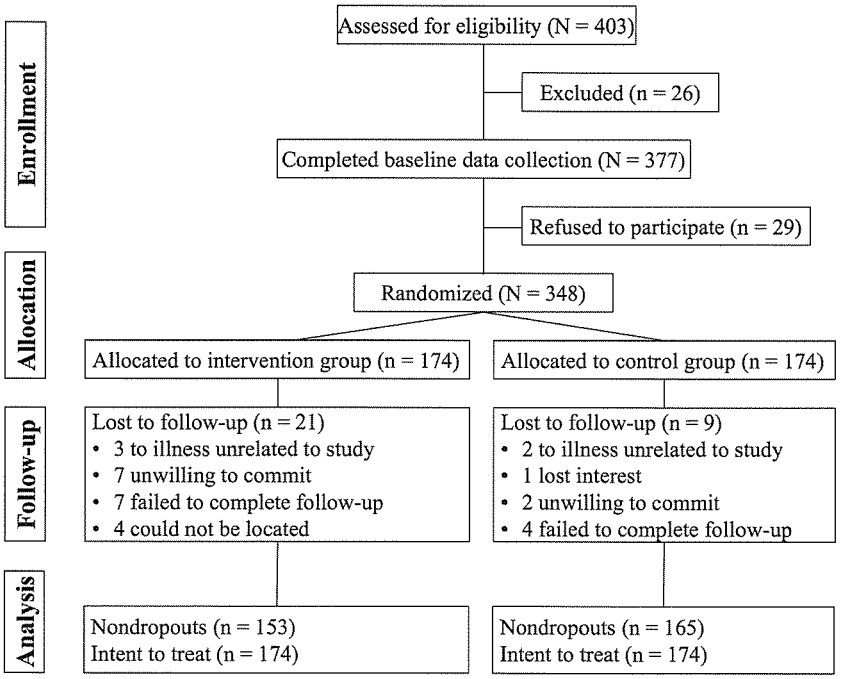

Fig. 1. Process for a therapeutic lifestyle modification intervention on a group of community volunteers, Rockford, IL. Note: The intervention and follow-up occurred from March through September 2003.

incorporated learning theory (behaviorism) in which changes in physical and dietary behaviors were promoted using health education and positive reinforcement. In addition to encouragement and positive feedback from staff, the CHIP alumni program was designed to help participants maintain positive behavior changes. The curriculum included the following topics: modern medicine and health myths, atherosclerosis, coronary risk factors, obesity, dietary fiber, dietary fat, diabetes, hypertension, cholesterol, physical activity, osteoporosis, cancer, lifestyle and health, the Optimal Diet, behavioral change, and self-worth.

The intervention group received a textbook and workbooks in conjunction with the CHIP lectures that closely followed the discussion topics and contained assignments with learning objectives that correlated with the discussion topics. These assignments were designed to assist the intervention group in understanding and integrating the concepts and information presented into their lives. Dieticians and medical professionals introduced the intervention group to current nutritional and medical information that related to the prevention of chronic diseases weekly.

The intervention group made dietary and physical activity goals, which they then were encouraged to follow. The dietary goal involved adopting a more plant-food-based diet that emphasized "as-grown," unrefined food. Prescribed foods included whole grains, legumes, vegetables, and fresh fruits. The diet was low in fat, animal protein, sugar, salt, very low in cholesterol, and high in fiber. The intervention group was also, accordingly with their new diet, encouraged to progressively work toward walking or exercising at a mild-to-moderate intensity for at least 30 min a day. A pedometer was given to the intervention group and they were encouraged to keep a physical activity log that recorded the miles they walked each day.

The primary objective of the health education intervention was to improve cognitive understanding of the importance of healthy lifestyles, nutrition and physical activity behavior, and risk factors associated with diabetes, hypertension, cardiovascular disease, and cancer.

Measures

Demographic (age, sex, race, marital status, annual family income, education) and selected cardiovascular risk factors were considered. Demographic information was collected at baseline. The cardiovascular risk factors were collected at baseline, 6 weeks, and 6 months. Measures included CRP levels, pedometer readings (step counts), weight, height, BMI, body fat percentage, and saturated fat.

Phlebotomists from the SwedishAmerican Health System's outpatient laboratory drew blood using a vacutainer (Becton-Dickinson Vacutainer Systems, Rutherford, NJ) after the participants had a 12-hour fast. Samples were allowed to clot and were then centrifuged. Clinical analyses were completed at the SwedishAmerican Health System laboratory. C-reactive protein was determined using a microplate protocol based on a latex bead enhanced immunoturbidity assay from the same technician and has been demonstrated to be a valid and reliable method (Wu et al., 2002; Otsuji et al., 1982; Rifai et al., 1999). Rifai et al. (1999) concluded that the Latex method was comparable to ELISA and can be used in research to determine CRP levels.

To determine the level of physical activity, a 7-day self-recorded pedometer log was maintained by each participant a week before measurements at baseline, 6 weeks, and 6 months. Participants from the intervention and control group wore the Walk4Life Model 2000 Life Stepper pedometer on a belt at the right hip directly above the right knee cap each day for 7 consecutive days. Immediately prior to going to bed the pedometer counts for the day were recorded and the number reset. Strike counts from pedometers are a valid and reliable method of monitoring and measuring free-living physical activity (Crouter et al., 2003; Beets et al., 2005; Tudor-Locke et al., 2005). Tudor-Locke et al. (2005) concluded that the time necessary to determine physical activity in a week with a pedometer was 3 days. Thus, the time taken from this study, 7 days, to determine physical activity was sufficient.

Weight and height were measured using standard medical weight and height scales calibrated by the Biometrics Department of the SwedishAmerican Health System. Body mass index (BMI) was determined using the formula weight (kg)/height $(m)^2$. Percent body fat was estimated using the Tanita TBF-300A electrical impedance scale, which has been shown to be a valid and reliable method (Kyle et al., 2001; Rubiano et al., 2000). Finally, saturated fat was estimated by the participants completing a self-administered food survey based on the 98-item Block questionnaire (Block et al., 1990; Hartman et al., 1996). Block et al. (1990) determined this type of questionnaire to be a valid method for determining saturated fat intake. Hartman et al. (1996) determined the reliability of this questionnaire to be adequate for research purposes.

Statistical analyses

Frequency distributions were computed and cross-tabulations used to perform bivariate analyses between intervention status (intervention vs. control) and selected demographic variables at baseline, with statistical significance based on the Chi-square test. Repeated measures analyses were performed on multiple measurements of selected response variables using the mixed models method. Also presented were results for the more conservative intent-to-treat method where individuals' baseline scores were carried over through the 6 month follow-up period. Regression analysis was used to evaluate the hypothesis that the intervention significantly lowers CRP and to assess the relationship between CRP and selected cardiovascular risk factors. Multiple regression was used to assess the simultaneous effect of these risk factors on CRP. The McNemar's test was used to evaluate changes in paired data from baseline to 6 weeks and from baseline to 6 months. The Cochran–Mantel–Haenszel test was used to evaluate the association between percent of high CRP among those in the intervention versus the control group, adjusting for CRP at baseline. This test was also used to compare high CRP status with whether BMI was decreased or not, adjusting for CRP at baseline. Analyses were performed using SAS version 9.1 (SAS Institute Inc., Cary, NC, USA, 2003). Statistical significance and confidence intervals were based on the 0.05 level.

Results

Of the 348 participants, ages ranged from 24 to 81 years (M=50.4, SD=11.0). The mean age for the intervention group

Table 1
Comparison of demographic characteristics of intervention and control groups in a therapeutic lifestyle modification program, Rockford, Illinois

Variable	Intervention		Control		χ^2 P value
	No.	%	No.	%	
Sex					
Male	47	27.0	51	29.3	0.63
Female	127	73.0	123	70.7	
Race					
White	167	96.0	160	93.0	
Black	4	2.3	10	5.8	0.23
Other	3	1.7	2	1.2	
Marital status					
Never married	12	6.9	20	11.6	0.39
Married	138	79.8	127	73.4	
Divorced	16	9.2	16	9.2	
Widowed	7	4.1	10	5.8	
Annual family income, $					
0 to <20,000	14	8.2	12	7.1	0.79
20,000 to <40,000	34	20.0	28	16.5	
40,000 to <60,000	37	21.8	41	24.1	
60,000+	85	50.0	89	52.3	
Education					
<High school	4	2.3	7	4.0	0.16
High school	37	21.5	46	26.6	
Some college	58	33.7	39	22.5	
Bachelor degree	39	22.7	38	22.0	
Post-bachelor degree	34	19.8	43	24.9	

Note: The intervention and follow-up occurred from March through September 2003.

Table 2
Selected cardiovascular risk factors at baseline, 6 weeks, and 6 months among participants in a therapeutic lifestyle modification program, Rockford, Illinois

Variable	Baseline mean	6 week mean	6 month mean	Mixed model F statistic P value		Intent-to-treat Wilks' lambda P value	
				Time effect	Time by group effect	Time effect	Time by group effect
Total steps/week							
Intervention	40,579	53,046	54,318	<0.0001	<0.0001	<0.0001	<0.0001
Control	43,869	46,063	49,513				
Body mass index							
Intervention	33.3	32.1	31.0	<0.0001	<0.0001	<0.0001	<0.0001
Control	31.4	31.2	31.1				
Weight, kg							
Intervention	93.3	90.1	87.0	<0.0001	<0.0001	<0.0001	<0.0001
Control	87.7	87.3	86.8				
% of Kcal from fat							
Intervention	36.7	27.7	28.2	<0.0001	<0.0001	<0.0001	<0.0001
Control	34.6	34.0	35.5				
Saturated fat, g							
Intervention	26.3	14.8	13.0	<0.0001	<0.0001	<0.0001	<0.0001
Control	21.8	19.0	20.2				

Note: The intervention and follow-up occurred from March through September 2003.

was 50.1 years compared with 50.8 years in the control group ($P=0.57$). Characteristics of the study participants are presented for selected demographic variables in Table 1. Distributions across the levels of each variable did not significantly differ between the intervention and control groups. The most common characteristic observed for each variable was: female, white, married, an annual family income of at least $60,000, and at least some college education.

Means for selected cardiovascular risk factors at baseline, 6 weeks, and 6 months are presented according to intervention status in Table 2. Each of these variables had a significant time effect and a significant group by time effect. Increase in total steps/week and decrease in each of the other cardiovascular risk factors was significantly greater for those in the intervention group.

At baseline, CRP was not associated with age, sex, race, marital status, income, or education. However, it was significantly negatively associated with total steps/week and positively associated with weight, BMI, and percentage of calories from fat (Table 3). In a multiple regression model with CRP regressed on total steps/week, weight, BMI, and percentage of calories from fat, only BMI remained statistically significant (slope=0.22; $P<0.0001$), explaining 28% of the variation in CRP. At 6 weeks, 14.7% of the variation in the change score for CRP was explained by baseline CRP (slope=−0.49; $P<0.0001$), 8.6% was explained by baseline BMI (slope=0.12; $P<0.0001$), and 0.7% (slope=0.29; $P=0.10$) was explained by change in BMI. At 6 months, 13.9% of the variation of change in CRP was explained by baseline CRP (slope=−0.52; $P<0.0001$), 9.8% was explained by baseline BMI (slope=0.13; $P<0.0001$), and 0.8% was explained by change in BMI (slope=0.16; $P=0.07$). Intervention status, age, sex, race, marital status, income, or education, total steps/week, percentage of calories from fat, saturated fat, and change scores in total steps/week, percentage of calories from fat, and saturated fat did not contribute to the significance of the model. These results are consistent with those obtained using the intent-to-treat method (data not shown).

The percentage of participants with high CRP fell from 46% (154/335) to 38% (124/329) at 6 weeks and 41% (127/312) at

Table 3
Mean risk factors according to C-reactive protein (CRP) at baseline among participants in a therapeutic lifestyle modification program, Rockford, Illinois

Risk factor CRP	Mean	P value
Total steps/week		
CRP low	52,015	<0.0001
CRP medium	43,068	
CRP high	36,444	
Body mass index		
CRP low	26.4	<0.0001
CRP medium	30.4	
CRP high	36.7	
Weight, kg		
CRP low	75.8	<0.0001
CRP medium	85.2	
CRP high	101.8	
% of Kcal from fat		
CRP low	33.3	0.0093
CRP medium	36.0	
CRP high	36.6	
Saturated fat, g		
CRP low	21.4	0.1568
CRP medium	23.5	
CRP high	25.6	

Note: The intervention and follow-up occurred from March through September 2003.

Table 4
Risk of high C-reactive protein (CRP) at baseline, 6 weeks, and 6 months according to baseline BMI among participants in a therapeutic lifestyle modification program, Rockford, Illinois

Time BMI	Relative risk	95% confidence interval
Baseline		
Normal	1.00	–
Overweight	1.55	0.88, 2.74
Obese	3.10	1.89, 5.11
6 weeks		
Normal	1.00[a]	–
Overweight	1.16	0.97, 1.39
Obese	1.30	1.10, 1.53
6 months		
Normal	1.00[a]	–
Overweight	1.15	0.94, 1.41
Obese	1.28	1.06, 1.55

Note: The intervention and follow-up occurred from March through September 2003.
[a]Adjusted for baseline levels of C-reactive protein.

6 months. The risk of high CRP (>3 mg/L) at baseline, 6 weeks, and 6 months is presented according to BMI in Table 4. At baseline, obese individuals were 3.1 times (210%) more likely to have high CRP than those with normal weight. At 6 weeks, obese individuals were 1.3 times (30%) more likely to have high CRP than those with normal weight, after adjusting for baseline CRP. Finally, at 6 months, obese individuals were 1.28 times (28%) more likely to have high CRP than those with normal weight, after adjusting for baseline CRP. These results are also consistent with those obtained using the intent-to-treat method (data not shown).

Discussion

Despite serum CRP levels being significantly associated with other cardiovascular risk factors at baseline, the intervention, which significantly improved these risk factors, did not discriminate CRP. This result is counter to those of two earlier studies that showed a reduction in CRP due to lifestyle interventions aimed at improving cardiovascular risk factors in coronary heart disease patients (Caulin-Glaser et al., 2005; Milani et al., 2004). However, these two studies focused on cardiac patients whereas the current study involved a generally healthy population.

Among both intervention and control participants in the current study, a significant positive association was observed between baseline BMI and CRP. Body mass index, in a normal population, often has a positive association with individual CRP levels because of its association with adiposity. Excess adipose increases inflammation and expression of CRP (Anty et al., 2006). Changes in CRP through 6 weeks and 6 months of follow-up were also associated with baseline BMI and CRP. Those with higher BMI at baseline showed a greater increase in CRP over time, whereas those with higher CRP at baseline showed a greater decrease in CRP over time. Change in BMI was marginally insignificantly associated with change in CRP, after adjusting for baseline BMI and CRP. In a randomized study design involving sedentary obese adolescents, those who gained weight compared with those who did not experienced significantly elevated circulating concentrations of CRP (Balagopal et al., 2005). Difference in the age group studied may explain why the effect of change in BMI in the current study had a small impact on change in CRP.

A recent cross-sectional study found that sports and exercise were negatively associated with CRP in men ($P<0.001$), and brisk walking was negatively associated with CRP in women ($P<0.001$) (Stamatakis et al., 2007). This is counter to another study where exercise was not associated with improved levels of CRP (Marcell et al., 2005). A negative association was found in the current study between total steps/week and CRP. However, after adjusting for BMI, this association became insignificant, which may suggest that BMI mediates the relationship between total steps and CRP. In a consistent manner, another study found that BMI, but not physical activity, predicted high-sensitivity CRP (Rawson et al., 2003).

Participants in the control group also experienced improvement in CRP, total steps/week, BMI, weight, and saturated fat, but to a lesser extent. Interviews with control group participants revealed that some were anxious to get started on improving their health behaviors and may have begun prior to starting CHIP 6 months after the intervention group. This allowed us to assess change in CRP according to BMI and other coronary risk factors for both intervention and control participants combined.

The participants in this study were mostly white and sufficiently self-motivated to volunteer to participate in the study. On average, participants were slightly more educated than the community average. Participants had lifestyles that permitted them to attend most, if not all, of the classes. This is evident by the high rate of attendance to this time-intensive program. Hence, findings of this study may differ from those based on cardiac patients or obese, inactive individuals. Another limitation was that the study was originally powered to detect anticipated intervention effects for BMI and exercise. A post hoc assessment revealed that the sample size was insufficient to identify a significant treatment effect on CRP at the small levels of change observed.

Conclusion

C-reactive protein at 6 weeks and 6 months was not significantly associated with the intervention. However, baseline levels of BMI and CRP were significantly associated with BMI and CRP. Higher BMI at baseline was associated with greater increase in CRP over time, but higher CRP at baseline was associated with greater decrease in CRP over time. For both intervention and control participants combined the percentage with high CRP (>3 mg/L) fell from 46% to 38% at 6 weeks and 41% at 6 months. Risk of high CRP at 6 weeks and 6 months after adjusting for baseline CRP was significantly greater for obese compared with normal weight. A longer trial and improvements in the methods for measuring CRP data should be considered in future studies.

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