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Apolipoprotein E Genotype and Gender Influence C-Reactive Protein Levels Regardless of Exercise Training Status

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Abstract

C-reactive protein (CRP) is a marker for systemic inflammation and increased cardiovascular disease risk. Regular exercise may decrease CRP. ApoE has three common genotype variants: E2/3, 3/3, and 3/4 that modulate lipid metabolism and may have other metabolic physiologic roles, including some evidence that the genotype affects CRP levels. We assessed fasting serum CRP in 117 (M=51, F=66) healthy adults who volunteered for a 6 month aerobic exercise program. Both pre and post-training measurements were available in 71 (M=31, F=40) subjects. At baseline and follow-up, numbers of subjects in the 3 groups were approximately equal: 2/3, n = 33 and 20; 3/3, n = 41 and 26; and 3/4, n = 43 and 25.

Results—At baseline, CRP levels differed by APOE genotype: means $\pm$ sd were 2.84 ± 2.18 , 2.59 ± 2.34 , and 1.90 ± 2.13 mg/L for E2/3, 3/3, and 3/4 subjects, respectively (3/4 vs. 2/3, $p < 0.05$). In women, CRP was higher than men (3.14 ± 2.49 vs. 2.12 ± 2.13 mg/L, $p < 0.006$). Exercise failed to affect CRP in the entire cohort (2.68 ± 2.38 vs 2.52 ± 2.48 mg/L), or in any APOE genotype group, and the APOE genotype effect observed at baseline persisted after training.

Conclusion—In a largely white study cohort CRP is higher in Apo E 3/3 than in 3/4 subjects and in women compared to men, but remains unchanged by 6 months of standard aerobic exercise training of the volume and higher intensity promoted by national organizations to reduce cardiovascular disease risk. How APOE genotype affects CRP is not known.

Keywords

APOE; C-reactive protein; aerobic exercise; gender

Introduction

Recent evidence suggests that inflammation contributes to the atherosclerotic process and that markers of inflammation, including C-Reactive Protein (CRP) are also risk markers for future

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atherosclerotic events¹. CRP is one of several “acute phase reactants” that include other markers such as fibrinogen and serum amyloid A that increase with inflammatory stress². Increased frequency of physical activity³ and higher aerobic fitness⁴ are associated with lower CRP concentrations. These observations suggest that regular physical activity potentially diminishes the systemic inflammatory response and is postulated to delay atherosclerosis.

Despite the strong evidence of a cross-sectional association between physical activity/fitness and CRP, few prospective longitudinal studies have determined if CRP decreases with aerobic exercise training (ET). Exercise training was seen to reduce CRP levels in previously trained individuals during preparation for a marathon⁵, but this volume of ET is far greater than the minimum required for health benefits⁶. The effect of such an exercise program with a lower volume of exercise on CRP levels is equivocal. One study observed a small, non-significant decrease (6%) in CRP in a group of weight stable individuals who had completed a supervised 6 months ET program⁷. Smith et al. showed a much larger decrease in CRP over 6 months (35%), but high baseline variability may have contributed to this change not being statistically different⁸. In contrast, data from the HERITAGE study were stratified according to baseline levels of CRP and showed that ET reduced CRP in those with high baseline (>3.0mg/L) CRP⁹. Therefore grouping individuals according to baseline levels of CRP and thus minimizing baseline variation might facilitate the observation of ET induced changes in CRP levels.

Little is also known about the effect of specific genetic variants on CRP levels. For example, Apolipoprotein E (ApoE) has three common protein-coding allelic variants, E2, E3, and E4 that have demonstrated to modulate lipoprotein metabolism in sedentary populations^{10;11} and the response to training¹². The presence of the apo E4 allele itself is a significant genetic risk factor for the early development of coronary artery disease¹³ much of which has been ascribed to its affect on lipid metabolism causing higher LDL levels¹⁴. However, recently additional mechanisms have been suggested including possible anti-inflammatory properties of ApoE¹⁵.

Apo E appears to protect vessels from atherosclerotic development induced by inflammation, as inferred from accelerated atherosclerosis in apoE null mice^{16;17}. In humans, CRP and plasma Apo E concentrations are negatively related¹⁸. Apo E genotype has been shown to partly determine plasma levels of Apo E, with E2 carriers having higher levels than E4 carriers¹⁹. Therefore it is possible that ApoE genotype might influence CRP levels. Contrary to the negative relationship between CRP and plasma apoE concentration, some epidemiologic studies have shown higher CRP in individuals carrying the E2 allele, or lower CRP in individuals carrying the E4 allele,²⁰⁻²⁶. Other studies show no effect of genotype²⁷⁻²⁹.

Therefore the purpose of this study was to examine the effect of Apo E genotype on CRP levels in sedentary adults. Secondly, since longitudinal studies measuring the response of CRP to exercise training are inconsistent, a further purpose was to examine the effect of supervised ET on CRP. Finally, since there is evidence that ET may decrease CRP specifically in those individuals with higher pre-training levels⁹, and Apo E genotype may affect CRP levels we examined the effect of Apo E genotype on the response of CRP to 6 months of supervised ET.

Methods

Study Overview

This study was conducted by the Exercise and Genetics Collaborative Research Group, a consortium of investigators at seven institutions. We recently completed a six-month aerobic exercise training study in volunteers recruited to create equal sized cohorts of the most common Apo E genotypes, which are E2/3, E3/3, and E3/4 and showed that both the increase in maximal oxygen uptake and decrease in the ratio of low to high density lipoproteins in response to ET

varied by Apo E genotype. The same study population were used to collect these data, the methods for which have previously been reported ¹².

IRB approval was granted at all institutions and written informed consent was obtained from all participants. In total 566 individuals were screened by genotype to create three cohorts equal for gender and for the three most common Apo E genotypes: Apo E 2/3, 3/3, and 3/4. Investigators were unaware of subjects' genotype and were only informed whether or not a subject qualified by genotype for inclusion. A total of 174 subjects initiated exercise training with 120 completing the six-month program. CRP measurements were only available on 117 of the 174 subjects at baseline and 73 of the 120 finishers, two of whom had levels high enough to indicate acute infection so were not included in the analysis. Therefore baseline data was analyzed on 117 participants and the effect of ET was analyzed on 71 of the finishers.

Subjects

Subjects were recruited if they were: healthy and without orthopedic problems, non-smokers, physically inactive, between 18 and 70 years of age, and consumed <2 alcoholic beverages daily. Subjects were considered physically inactive if they participated in vigorous activity <4 times/month for the prior 6 months. Subjects with diagnosed metabolic abnormalities or who were taking medications known to affect CRP levels were excluded from the study. Subjects underwent a medical history, physical exam, and a maximal exercise test to detect unreported abnormalities and occult coronary artery disease. Race has been shown to affect CRP levels ^{30;31} so it is important to state that the study population was largely white. Characteristics of the subjects are shown in Table 1.

Apo E Genotype Determination

DNA was extracted from leukocytes and Apo E variants determined using standard techniques ³².

Serum CRP Measurements

One fasting serum sample was obtained after a 12 hour fast before the start and after six months of exercise training. Post-training samples were obtained within 24 hours of the penultimate and final exercise training sessions. CRP was assayed via rate Nephelometry using a high sensitive, two-site chemiluminescent enzyme immunometric assay with one monoclonal and one polyclonal anti-CRP antibody. This method has been standardized against the WHO International Reference Standard for CRP Immunoassay ³³ and validated against the method approved by the FDA for use in assessing the risk of cardiovascular and peripheral vascular disease ³⁴. CRP levels in women before and after training were obtained during the first ten days of the menstrual cycle to avoid possible variations in values.

Anthropometric Measurements

Body weight and height were measured using balance beam scales and wall mounted tape measures. Waist girth measurements were taken using a cloth tape measure at the narrowest portion of the torso between the umbilicus and xiphoid process ³⁵.

Insulin Resistance

Insulin resistance was not directly measured, but estimated from fasting glucose and insulin values using the Homeostasis Model Assessment method ³⁶.

Maximal Exercise Capacity

Subjects underwent two pre and one post-training maximal treadmill exercise tests. The first pre-training test was designed to detect occult ischemia and to familiarize subjects with the

measurement protocol, but was not used in data analysis. The second pre-training test and the post-test used the modified Åstrand protocol³⁷. Blood pressure and 12-lead electrocardiogram, as well as expired oxygen, carbon dioxide, and ventilatory volume were measured. Each test site used its own metabolic measurement system for cardiorespiratory measurements and followed manufacturers' calibration procedures. Maximal oxygen uptake was defined as the average of the two highest consecutive 30-second values at peak exercise.

Dietary Control Procedures

Tchernof et al. recently showed that CRP levels were reduced in response to weight loss from calorie restriction³⁸. Therefore to assess the unmasked effects of ET subjects were asked not to change their usual dietary composition throughout the study in an effort to maintain their original weight. Dietary calories and composition were assessed by random, 24-hour dietary recall^{39;40}. Trained dietitians called the subjects by telephone on one weekday and one weekend day before the start and during the last month of exercise training. Results from the two calls were averaged to estimate dietary intake.

Exercise Program

Subjects underwent a six-month, progressive, supervised exercise program. Exercise session duration was increased from 15 to 40 minutes during the first four weeks. Subjects exercised between 60 and 85% of their maximal exercise capacity based on pre-training maximal heart rate. Once subjects could perform 40 minutes of exercise, they continued this duration of exercise four days a week for an additional five months. Subjects also participated in five minutes of warm-up and cool-down so that each workout required 50 minutes. The primary mode of exercise was performed on a treadmill, but a variety of other modalities including stationary cycles, cross-country ski machines, stair steppers, and rowing machines were also available.

All the subjects' exercise sessions were monitored by exercise physiologists to ensure the appropriate levels of frequency, duration and intensity were attained. Upon arriving at the training facility all participants had to sign in at the beginning of each session. They were then given a heart rate monitor that was used to ensure exercise was being performed at the appropriate intensity. Prior to signing out each participant handed their heart rate monitor over to the exercise physiologist who recorded the average heart rate for that session. Failure to meet the stated limits resulted in removal from the study.

Data Analysis

CRP data were log transformed to normalize the positively skewed distributions seen in men, women, and within APOE genotype groups. Lakka et al. showed that women have higher CRP levels than men, therefore gender was also selected as a dependent variable⁹. To test for ApoE, gender, and a possible interaction effect at baseline, we applied a 3 (Group) $\times$ 2 (Gender) analysis of variance using the GLM model (SPSS v10.1) to accommodate different sample sizes across gender and Apo E genotype. To test for the effect of exercise, a 3 (Group) $\times$ 2 (Gender) $\times$ 2 (Exercise, pre and post) repeated measures analyses of variance (ANOVA) was used. Analysis of covariance was used to eliminate the effects of BMI and VO₂max on the CRP results. Sidak's adjusted post hoc tests were employed when F ratios were significant. Significance levels were two-sided with $\alpha = 0.05$.

RESULTS

The Effects of Apo E genotype and Gender on Baseline CRP Levels

Both gender (Figure 1) and Apo E genotype (Table 2) showed independent effects on baseline levels of CRP. Subjects with the Apo E 3/4 genotype had lower CRP values than either the Apo E 2/3 or 3/3 groups ($p \leq .05$). Figure 1 shows CRP values for men and women and reveals a significant gender effect with women having higher CRP than men ($p < 0.05$). However, there was no gender by Apo E genotype interaction ($p > 0.05$).

The Effect of 6 Months of ET on Cardiovascular Fitness and Anthropometric measures

Six months of ET resulted in an overall increase in $\text{VO}_{2\text{max}}$ (30.75 ± 7.09 vs 33.61 ± 8.32 ml/kg/min, $p < 0.001$). As has previously been reported from this cohort, ApoE genotype did influence the magnitude of change in $\text{VO}_{2\text{max}}$ ¹². There were also observed reductions in body mass (-1.24 ± 3.63 kg, $p < 0.01$) and waist circumference (-1.65 ± 4.27 cm $p < 0.001$) and no change in insulin resistance, all of which were unaffected by Apo E genotype (time X genotype interaction, $p > 0.05$). Diet composition was unchanged over the study period (data not shown).

The Response of CRP to 6 months of ET: The Effect of Apo E genotype and Gender

The results of the repeated measures ANOVA suggest that the rate of change in CRP values due to six-months of ET was not statistically different for either ApoE genotypes (2/3, 3/3, and 3/4) or gender groups ($p > .05$). Indeed, 6 months of ET, overall, was not observed to significantly lower CRP values to a statistically significant degree ($p > .05$). Furthermore the gender by Apo E genotype interaction did not exhibit statistical significance ($p > .05$).

Discussion

In the present study, individuals with the Apo E4/3 genotype had lower CRP at baseline, prior to training. In addition men had significantly lower CRP levels than women. In the entire cohort 6 months of ET with minimal weight loss and no change in insulin resistance failed to reduce CRP levels. Further, despite the baseline differences in CRP across Apo E genotypes, no genotype effect was seen on the CRP response to training.

These results contrast with prior cross-sectional reports demonstrating that CRP is lower in more physically active or more physically fit individuals^{3;4}. While there is evidence that ET reduces CRP levels it is questionable whether this was due to concomitant weight loss⁴¹⁻⁴³. Body mass is a major determinant of CRP with levels being increased in obesity, especially if the subjects are also insulin resistant^{44;45}. The evidence of a causal relationship is strengthened by the observation that weight loss leads to reductions in CRP³⁸. Therefore it can be difficult to evaluate the impact of exercise, which is often accompanied by weight loss, on CRP levels. The present study was designed so that participants would remain weight stable over the six month training period, therefore allowing us to observe the effects of exercise *per se* along with ApoE genotype. Despite this design, small, but significant decreases in body weight and waist circumference were observed. However, these were likely to be metabolically insignificant as evidenced by the lack of change in insulin resistance.

There is considerable variability within the general population in CRP values, which poses a problem when investigating interventions designed to alter CRP levels. Specifically an insufficiently small sample size given the variability may increase the risk of a type II error. In a group of recreational runners, a relatively homogenous population in terms of CRP, 9 months of marathon preparation resulted in a small absolute change in CRP (1.19 to 0.82 mg/L) but one that was statistically significant⁵. In contrast, the much larger decrease (although

a similar percentage decrease) observed by Smith et al (4.18 to 3.13 mg/L) was not statistically significant in their more heterogeneous cohort⁸. As such, we took measures to try and minimize variability in baseline CRP levels such as exclusion of participants with diagnosed metabolic disorders such as diabetes, those who were on medications that have been shown to affect CRP and finally eliminated all participants whose baseline or post training CRP values were above 10mg/L, a value indicative of acute infection. That, coupled with our relatively large sample size, gives us confidence that the lack of change in CRP with 6 months of ET (2.68 to 2.52 mg/L) is real and not a statistical anomaly and is in agreement with some previous longitudinal studies^{7;8}.

The subjects in the previously cited study by Mattusch et al. were recreational runners who increased their running from 32 to 53 km/wk in preparation for participation in a marathon⁵. Recreational runners typically exercise 5-6 times per week, sometimes at high intensity. Such intensity and volume, greater than in the present study, may be required to lower CRP and may explain the difference in results compared to the present study and suggest a threshold may exist for ET induced reductions in CRP to be observed. If true, these data suggest that an exercise program designed to meet the minimum levels required to deliver the health benefits as recommended by the CDC is not sufficient to meet this threshold. However, we were able to collect training HR data on 66 of the 71 individuals with post training CRP data and investigated the possibility that there were different responses between those who habitually exercised at the lower end compared to the higher end of the intensity range. The bivariate correlation between change in CRP and average training HR was 0.009. We also split the cohort in half, into tertiles and quartiles according to training HR and in no case were within group differences observed. In no instance was any statistical significance observed. Therefore there is nothing to suggest that actual training intensity affected the CRP response in the present study.

The HERITAGE study showed that CRP was not universally reduced as a result of a 20 week aerobic exercise intervention⁹. However, when participants were grouped according to baseline levels of CRP, those with the highest level significantly reduced CRP independent of changes in body weight. Abdominal and visceral fat is highly associated with the systemic inflammation associated with the metabolic syndrome⁴⁶. Recent evidence suggests that exercise can reduce fat storage in this depot without an overall improvement in body weight^{47;48}. Such observations provide a rationale for the sometimes-observed decrease in CRP independent of weight loss. Although not reported in the specific cohort, it stands to reason that the high CRP group in the HERITAGE study may have had higher baseline abdominal and visceral fat levels than the other groups. It can therefore not be ruled out that the non-universal changes in CRP observed in this cohort could have been explained by differential changes in these two fat depots that were not manifested through measurement of body mass. In the present study despite the statistically significant reduction in waist circumference, the practical decrease was negligible and was accompanied by no change in levels of insulin resistance.

It has been several years since Manttari et al. first showed the unexpected negative relationship between the ApoE4 allele and CRP²². Most subsequent reports have confirmed this finding^{20;21;23-26}, but not all²⁷⁻²⁹. The present study agrees with the original findings, but the reason for the negative relationship between the ApoE4 allele and CRP is still unclear. Plasma Apo E concentrations are genotype dependent with E3/E3 being intermediate between the higher E3/E4 and lower E2/E3¹⁹. Apo E has been shown to specifically down regulate TNF alpha production in the central nervous system⁴⁹ and modulate systemic levels of proinflammatory cytokines⁵⁰ which partly explains the relationship between the E4 allele and the development of atherosclerosis¹³ and Alzheimer's disease⁵¹, both in part inflammatory processes. However, this might lead to a hypothesis that CRP would be lowest in those with

E2 and highest in those with E4, but the present data suggest the contrary. This finding persisted even after adjustment for BMI so it is unlikely to have been mediated by pathology linked to differences in body weight.

A limitation of the present study is the fact that APOE 2/3 and E4/3 genotypes were overrepresented in the present study. Expected population frequencies of E3/3, E2/3, and E4/3 genotypes are 65-70%, 5-10%, and 10-15%, respectively. The genotype distribution in the present study was 28%, 35%, and 37%. Caution must be taken when generalizing our results to the population. Additional, larger studies of this relationship are therefore required. Also, there are no prospective studies of the effects of high intensity, high volume exercise training on CRP. CRP levels have been shown to be affected by modifications of the endocrine environment, such as oral contraceptive use and hormone replacement therapy (HRT)²¹. The number of women on HRT in our cohort was too small (n=4) to perform any further analysis, but excluding their data from the analysis had no effect on the outcome. Furthermore, we only had incomplete data on oral contraceptive use, which could be seen as a limitation to the present study.

These data are from a primarily white cohort. However, a preliminary analysis of the data suggested that race interacted with Apo E genotype to affect CRP values ($p \leq .05$). Closer inspection of the results revealed that the CRP values of the three non-White participants, increased overall as a result of regular ET while the CRP values of the White participants decreased. Since the number of non-White participants was too small for the interaction to be studied closer, their scores were not analyzed further. While race has been shown to influence CRP levels^{30;31} and that it affects the relationship between physical fitness and CRP levels⁵² no study has shown race to affect how CRP responds to ET. This requires further study. However, these data do confirm the observation that CRP levels are higher in women than in men^{9;26}.

A strength of the present study was that every exercise session was monitored by an exercise physiologist to ensure the exercise prescription was being met. This strict enforcement did result in a drop out rate of approximately 30% over the course of 6 months, but was required to ensure that only those who were doing the appropriate exercise training were included in the results of a study investigating the effects of exercise training per se. As such, these data suggest 6 months of ET does not alter CRP levels in individuals who maintain baseline levels of insulin resistance despite improvements in cardiorespiratory fitness and modest reductions in body mass and waist circumference. Furthermore, these data confirm the findings that both the ApoE4 allele and male gender are associated with lower values of CRP. Despite the previous observation that baseline CRP levels play a role in the response to aerobic exercise training, neither the baseline effect of the ApoE genotype nor gender were sufficiently large to affect the response to exercise in this cohort.

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Figure 1.

Differences in C-Reactive protein between men and women in a group of 117 participants who started the study (M=51, F=66) and in the group of 71 participants who completed the study (M=31, F=40).

* Significantly different than Men, $p < 0.05$

Table 1
Baseline characteristics of all subjects at baseline and those who completed the six months of aerobic training (finishers). Data are expressed as means $\pm$ S.D (range)

	N	Age	Height (cm)	Weight (kg)	BMI (kg/m ²)	Waist Circumference (cm)
All Subjects	117	37.4 $\pm$ 11.6 (18-62)	170.4 $\pm$ 9.8 (152-193)	81.7 $\pm$ 17.1 (47.7-138.6)	28.0 $\pm$ 4.7 (17.3-40.3)	88.8 $\pm$ 14.3 (59.7-134.6)
Women	66	38.2 $\pm$ 11.6 (18-62)	164.3 $\pm$ 6.6 (152-185)	73.8 $\pm$ 13.4 (47.7-101.8)	27.3 $\pm$ 4.5 (18.3-38.0)	82.6 $\pm$ 11.7 (59.7-120.1)
Men	51	36.4 $\pm$ 11.5 (18-56)	178.3 $\pm$ 7.2 (152-193)	92.0 $\pm$ 15.9 (62.7-138.6)	28.9 $\pm$ 4.7 (17.3-40.3)	97.0 $\pm$ 29.2 (67.056-134.6)
Finishers	71	40.0 $\pm$ 11.5 (18-62)	171.6 $\pm$ 1.0 (152-193)	83.4 $\pm$ 18.5 (50.0-138.6)	28.1 $\pm$ 4.7 (19.7-40.3)	91.2 $\pm$ 14.7 (64.3-134.6)
Women	40	40.0 $\pm$ 11.9 (20-62)	165.0 $\pm$ 0.07 (152-185)	73.7 $\pm$ 13.0 (50.0-101.8)	27.0 $\pm$ 4.2 (19.7-37.4)	83.8 $\pm$ 11.7 (64.3-120.1)
Men	31	40.1 $\pm$ 11.3 (18-56)	180.1 $\pm$ 6.0 (169-193)	96.0 $\pm$ 17.0 (65.0-138.6)	29.6 $\pm$ 4.9 (20.9-40.3)	100.7872 $\pm$ 2.3 (77.5-134.6)

Data are presented for baseline CRP (mg/L) levels in all subjects and only those who completed 6 months of exercise training. Post training CRP levels are presented only for the subsection of subjects who complete the training. The effect of ApoE genotype is shown.

Table 2

All Subjects		N	Baseline	Subjects who completed exercise training		Δ
N				Baseline	Post Training	
E2/3	33	20	2.84 ± 2.18	3.09 ± 2.36	2.98 ± 2.43	-0.11 ± 1.84
E3/3	41		2.59 ± 2.34	3.05 ± 2.38	2.96 ± 2.69	-0.09 ± 2.63
E4/3	43		1.90 ± 2.13	1.99 ± 2.34	1.71 ± 2.15	-0.28 ± 2.10
Total	117	71	2.40 ± 2.24	2.68 ± 2.38	2.52 ± 2.48	-0.17 ± 2.22

* p < 0.05, significantly different from E2/3.

† p < 0.05, significantly different from E2/3 and E3/3.