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Effects of exercise on c-reactive protein in healthy patients and in patients with heart disease: A meta-analysis

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ABSTRACT

Decreases in circulating hsCRP have been associated with increased physical activity and exercise training, although the ability of exercise interventions to reduce hsCRP and which individuals benefit the most remains unclear. This meta-analysis evaluates the ability of exercise to reduce hsCRP levels in healthy individuals and in individuals with heart disease. A systematic review and meta-analysis was conducted that included exercise interventions trials from 1995 to 2012. Forty-three studies were included in the final analysis for a total of 3575 participants. Exercise interventions significantly reduced hsCRP (standardized mean difference −0.53 mg/L; 95% CI, −0.74 to −0.33). Results of sub-analysis revealed no significant difference in reductions in hsCRP between healthy adults and those with heart disease ($p = .20$). Heterogeneity between studies could not be attributed to age, gender, intervention length, intervention type, or inclusion of diet modification. Exercise interventions reduced hsCRP levels in adults irrespective of the presence of heart disease.

Introduction

Circulating levels of high-sensitivity c-reactive protein (hsCRP) is a modifiable risk factor for cardiovascular disease (CVD).[1,2] hsCRP was found to be an independent predictor of CVD in a cohort study of 15,792 adults, ages 45–64 years, designed to identify whether hsCRP levels in middle-aged adults was associated with future risk of CVD.[3] The authors went on to state that hsCRP may be a good early predictor of CVD even when other traditional risk factors, such as high levels of low-density lipoprotein C (LDL-C), are not present. In another cohort of 3345 German men, the authors found that hsCRP levels were associated with risk of CVD independent of the Framington Risk Score (FRS), and enhanced the prognostic value of the FRS in persons with intermediate risk for CVD.[4]

Decreases in circulating hsCRP have been associated with lifestyle changes including changes in diet[5–8] as well as increased physical activity[9–14] and exercise training.[15–20] Although accumulating evidence supports the clinical use of hsCRP measurements in healthy individuals to direct preventative treatment regimens, questions remain as to whether exercise interventions reliably reduce hsCRP and which individuals are most likely benefit from programs aimed at reducing circulating levels of hsCRP. Epidemiological studies in patients diagnosed with heart disease as well as in healthy individuals have shown that increased physical activity is associated with decreased levels of hsCRP as well as lower risk of heart disease[14,21–28]; but, these studies are retrospective in nature and depend on self-report measures of physical activity. Controlled studies in patients with diagnosed heart disease have shown that exercise training is associated with reduced circulating hsCRP[29]; yet, results in healthy people have been inconclusive.[20,30–34] The most recent meta-analysis suggested that hsCRP is not lowered in healthy adults enrolled in an aerobic exercise program ($M \pm SEM = -0.11 \pm 0.14$ mg/L, 95% CI: −0.39 to 0.17 mg/L), but at that time only 5 clinical trials met the inclusion criteria.[30] A recent meta-analysis in persons diagnosed with heart disease revealed that an exercise intervention is associated with lower hsCRP levels (Standardized Mean Difference (SDM) = −0.345, 95% CI: −0.444 to −0.246); but the meta-analysis included studies that were pre/post-design with no control group.[29]

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There are several explanations for the inconsistent results observed in studies examining the potential of exercise to lower hsCRP. Gender differences in hsCRP levels have been observed, with higher hsCRP levels being associated with intima-media-thickness, a measure of early artherosclerosis, in women but not in men.[35] Additionally, decreases in hsCRP level due to an exercise intervention have been observed in obese individuals with glucose intolerance in the absence of cardiovascular disease.[36] There is research suggesting that increasing fitness is not associated with lowered hsCRP, but lowered hsCRP following exercise intervention can be explained by resultant reductions in weight.[37] Finally, baseline hsCRP may be elevated in patients who have recently experienced a cardiac event,[38] and post exercise levels of hsCRP may be elevated in the period directly following intense exercise.[39]

The primary goals of this meta-analysis were to determine if exercise reduces hsCRP in healthy adults and in individuals with heart disease, and to determine if the reduction is significantly different between groups. A secondary goal of this study was to determine factors that may lead to variance in the intervention effect not explained by chance (i.e., study heterogeneity). The following factors were reviewed: age, gender, intervention duration, intervention type, inclusion of diet in the intervention, timing of blood draws, and presence of risks associated with metabolic syndrome.

Methods

Data sources

Studies for this systematic review and meta-analysis were retrieved through computerized literature searches of PubMED and The Cochrane Central Register of Controlled Trials as well as cross-referencing of review articles and retrieved studies. Keywords used in the search included exercise, physical activity, c-reactive protein, coronary heart disease, cardiovascular disease, inflammation, clinical trials, and adults. The study results were reported using the PRISMA framework, with the exception of the abstract.

Inclusion criteria

Studies performed between the years of 1995 and 2012 were included in the systematic review and meta-analysis if they met the following criteria: 1) randomized and non-randomized trials; 2) exercise intervention $\geq$4 weeks but $\leq$3 years; 3) assessment of hsCRP at baseline and following the last exercise session; 4) human subjects $>$18 years of age; 5) inclusion of control group that did not receive an exercise intervention; 6) studies of healthy adults and/or adults with ischemic heart disease and heart failure without other significant disease processes; and 7) English language studies published in scientific journals. The earliest search date was set at 1995 due to the availability of reliable assays to assess hsCRP levels in blood serum.[40] The time frame for the exercise interventions was chosen based on similar inclusion criteria used in a prior meta-analysis of randomized trials in healthy adults.[30] Study selection did not include articles in foreign-languages due to concerns regarding translation of results, and it was decided to only include scientific journal articles to ensure inclusion of quality studies.

Data abstraction

An electronic spreadsheet was created to record data from the studies reviewed. Categories that were coded included study characteristics (e.g., source and date), subject characteristics (e.g., age, gender, and health status), exercise training program characteristics (e.g., duration and frequency), change in hsCRP (mg/L), and hsCRP assessment procedure (e.g., time before and after exercise). Subject health status data included abstraction of indicators of metabolic syndrome in accordance with International Diabetes Foundation's (IDF) consensus statement on metabolic syndrome,[41] which defines metabolic syndrome as having central obesity (BMI $\geq$ 30 kg/m^2) and at least two of the following: 1) raised triglycerides ($\geq$150 mg/dL or treatment for such), 2) reduced high-density lipoprotein (HDL) cholesterol ($<$40 mg/dL in males, $<$50 mg/dL in females, or treatment for such), 3) high blood pressure (systolic $\geq$130, diastolic $\geq$85, or treatment for such), and 4) raised fasting glucose ($\geq$100 mg/dL or diagnosis of type II diabetes). A literature review was conducted by the research assistant. Data were abstracted and eligibility was determined by two reviewers. Discrepancies in the data were resolved by consensus.

Statistical analysis

For each study included in the meta-analysis, the mean difference in hsCRP was calculated by subtracting the change difference in the control group from the change difference in the intervention group. A random effects model was used to estimate the standard mean difference in change from baseline for hsCRP. The random effects model was chosen because of its ability to statistically control for heterogeneity as well as to provide for wider 95% confidence intervals (CI) than the fixed-effects model when significant heterogeneity is expected. Ninety-five percent CI were used to establish statistical significance of the results. If the results did not cross zero, they were considered to be significant. Heterogeneity was also examined using the I^2-statistic, which is a measure of intervention effect due to known differences in study design.[42]

Analyses of interaction effects (moderators) for several a priori explanatory variables were conducted. The interaction effects examined included age, gender, duration of exercise intervention, and type of exercise intervention. A subgroup analysis to determine difference in effect for healthy adults versus adults with cardiac disease was also conducted. A one-way, random effects ANOVA model was used to estimate the standard error and variance for each group and to test whether these means were different between groups. It was assumed that the variance among each group was different. Prior to performing the analysis, the moderators were categorized. Interaction effects due to presence of factors related to metabolic syndrome and timing of blood draws was not conducted due to insufficient information within the individual studies.

The quality of the studies was assessed using a previously developed 5-point scale that has been shown to be both reliable and valid.[43] The scale ranges from 0 to 5 with higher scores representing greater study quality.

In cases where the standard deviation for the change in hsCRP was not reported, it was imputed using the following formula[44]:

$$SD_{\Delta} = \sqrt{SD^2_{Baseline} + SD^2_{Final} - (2{*}Corr{*}SD_{Baseline}{*}SD_{Final})},$$

where "Corr" is the correlation coefficient between the standard deviations for the baseline and the standard deviations for the final measures of hsCRP in both the experimental and control groups derived from studies with known standard deviation for change. Corr for both the experimental and control groups were calculated as follows:

$$Corr = \frac{SD^2_{baseline} + SD^2_{final} - SD^2_{change}}{2\,x\,SD_{baseline}\,x\,SD_{final}}$$

The correlation coefficients were averaged to obtain a Corr equal to 0.80. The averaged Corr was included in the equation to impute the standard deviation for hsCRP.