

Clinical Applications

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Exercise – The New Penicillin: *Inflammation and Chronic Disease*

Conventional wisdom for years has led us to believe that peptic ulcers were the consequence of stress or spicy foods and that cardiovascular disease was caused in large part by a sedentary lifestyle, poor nutrition, and smoking. Few would have believed then that bacteria could play any part in causing either of these two diseases. The cause of peptic ulcers is now known to be the result of an infection that is caused by bacteria called *Helicobacter pylori*. This bacterial relationship was discovered in 1982 when two Australian researchers found that up to 80 percent of patients with ulcers were infected with the H. pylori bacteria. This is now common knowledge among the medical community but few individuals are even aware of the fact that bacterial infection can also be connected to cardiovascular disease through what researchers call *chronic sub-clinical* infections. The focus of this paper is to demonstrate that the causal factors in the development of cardiovascular disease are now thought to go beyond genetics and lifestyle, and may now include the influence of bacterial infection.

Inflammation and Cardiovascular Disease.

The response-to-injury hypothesis of atherosclerosis was proposed over 25 years ago and it suggests that damage to the endothelium of the arteries causes the lesions that eventually develop into atherosclerotic plaque. *C. pneumoniae* is one of the infectious microorganisms responsible for endothelial damage while we are most familiar with other more traditional causes such as elevated LDL; free radicals caused by cigarette smoking, hypertension, and diabetes; genetic alterations; elevated plasma homocysteine levels.

Chronic infection is commonplace in our population today and it is known that upwards of 70% of adult women and 80% of adult men by age 65 test positive for the bacterial pathogen *C. pneumoniae*. This pathogen has been implicated in the atherosclerotic process, perhaps by interacting with other traditional risk factors. Since antibiotics are not being used to treat this infection, there is growing interest in how lifestyle behaviors may interact with this inflammatory process to reduce the risk of developing cardiovascular disease.

Inflammatory Markers and Cardiovascular Disease.¹

The inflammation that is caused by bacterial pathogens produces elevations of different markers in the blood, the most studied of which is *C-reactive protein* (CRP). In fact, a recent study by Ridker and others¹ found that CRP was a stronger predictor of cardiovascular events than LDL cholesterol level. In addition, it added significant additional prognostic ability to the traditional risk factors commonly used in the widely accepted Framingham risk score. The powerful predictive value of CRP is demonstrated in Figure 1 which reveals that elevated CRP levels actually have twice the predictive value as lipoproteins, and when combined with the TC:HDL Ratio (ratio of Total Cholesterol to HDL), this predictive capacity is even further enhanced.

Insert Figure 1.

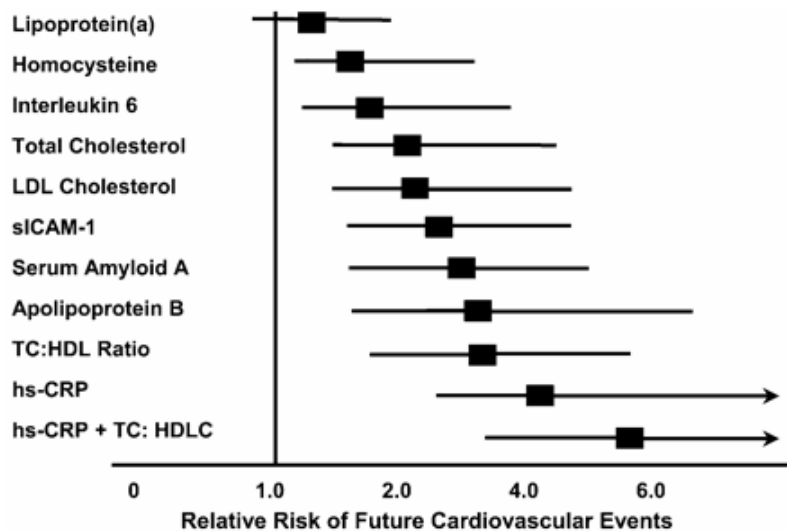


Figure 1. Direct comparison of CRP to several other lipid and non-lipid risk factors for cardiovascular disease. [from: Ridker PM. Clinical application of C-reactive protein for cardiovascular disease detection and prevention. *Circulation*. 2003;107(3):363-9.]

C-Reactive Protein and Chronic Disease.

The search for causes outside of the traditional risk factors in the prediction of cardiovascular disease is prompted by the fact that nearly half of all myocardial infarctions occur in individuals with a low to moderate risk lipid profile. Saito and others² studied the relationship between CRP and the traditional risk factors for CHD and found that, compared to individuals without any disease, levels of CRP were significantly higher in individuals with documented hypertension, diabetes mellitus, and coronary heart disease. So it appears that CRP is elevated in chronic diseases other than just cardiovascular disease.

A clustering of risk factors known as the “metabolic syndrome” is also predictive of future cardiovascular events; these factors include: upper-body obesity, hypertriglyceridemia, low HDL, hypertension, and abnormal blood glucose. It is not surprising that individuals with the metabolic syndrome are usually overweight, sedentary, have a high risk of diabetes, and are characterized by insulin resistance. Ridker and others³ found that as individuals accumulate these components of the metabolic syndrome, there is a progressive increase in the levels of CRP, thus making CRP a marker of inflammation that is common not only to heart disease, but to obesity, diabetes, and stroke as well.

Physical Activity, Weight Loss, and C-Reactive Protein.

Now that we know that CRP is related to chronic diseases such as obesity, diabetes, and heart disease, the next question is whether CRP can be modified by changes in obesity and physical fitness through weight loss and/or physical activity. The good news is that the physically active individuals with normal body weight have the lowest levels of CRP when compared to those who are sedentary and overweight. The relationship between CRP vs. fitness and fatness has been studied in both cross-sectional studies and longitudinal studies.

Weight Loss and CRP. While several studies have shown that progressively higher CRP levels were found in individuals with higher BMI, waist girth, fat mass, and visceral adipose tissue, there are two recent studies are encouraging with respect to the change in CRP with weight loss: Heilbronn and others ⁴ found a 26% reduction in CRP in 83 healthy obese women who lost 7.9 kg following caloric restriction while Tchernof and others ⁵ demonstrated a 32% fall in CRP values in 25 obese postmenopausal women who lost 15.6% of their body weight. Both studies showed that the changes in CRP were also closely correlated with the changes in weight loss.

Physical Fitness, Physical Activity and CRP. The relationship between physical fitness and CRP has been demonstrated in several studies: Church and others ⁶ found that the level of CRP in participants in the highest quintile of fitness had CRP levels that were nearly 80% lower than the CRP levels of those in the lowest fitness quintile. Similar results were found by LaMonte and others ⁷ who found significantly lower CRP levels (-47%) in women with the highest level of cardiorespiratory fitness compared to those in the lowest fitness group; additionally, those women with smaller waist girths and BMI levels also had proportionally lower CRP levels. These trends have been demonstrated in several other recent studies as well, confirming the favorable influence of physical fitness upon CRP levels.

In contrast to physical fitness, several large scale cross sectional studies have examined the influence of **physical activity** levels on CRP values. Abramson and others ⁸ studied 3,638 apparently healthy adults and found that more frequent physical activity was independently associated with lower CRP levels. They discovered that those individuals who engaged in physical activity 22 or more times per month had a 37% lower CRP levels than those who were active fewer than 3 times per month. Similar results were obtained by several other investigators who have demonstrated that the most physically active men and women have CRP levels significantly lower than those in the less active and sedentary groups. Finally, in a very large-scale national study, Ford ⁹ analyzed the results from the NHANES Survey III using 13,748 adults ≥ 20 years of age and found a progressive decrease in CRP levels with increasing levels of physical activity. The most active group had CRP levels that were nearly 50% lower than those found in the sedentary group.

Exercise Training and CRP. The studies cited above were retrospective cross-sectional studies; however, a recent study is very important because it is prospective in nature, i.e., this is a study that evaluates participants both before and after an exercise training program. Such a study was conducted by Smith and others ¹⁰ who followed 43 middle-aged (49.7 yrs) men and women who trained 2.5 hours/week for 6 months. They found a 35% decrease in CRP levels while there was no change in a control group. Other prospective studies have found similar results and confirm the beneficial effects of regular exercise upon the CRP in adults.

The Bottom Line.

The role of chronic infection in the development of cardiovascular disease is becoming increasingly clear but we do not have all the answers yet. There are no long-term clinical trials that have demonstrated that reducing the levels of CRP in those individuals with elevated levels will have a protective effect upon cardiovascular disease. These studies need to be done before we can say with any degree of certainty that there is a causal effect. What we do know is this:

- Losing weight through caloric restriction and/or physical activity is beneficial since it reduces circulating insulin levels, which in turn lowers CRP levels and the subsequent risk of diabetes and cardiovascular disease.
- Regular moderate to vigorous exercise is beneficial because it too lowers serum insulin levels, causes improved changes in the constituencies in the blood (CRP as well as several clotting factors), and improves responsiveness of the endothelium. In combination, these changes reduce atherosclerotic plaque development and the risk of cardiovascular disease.

References.

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