C-REACTIVE PROTEIN AS A MEASURE OF CARDIOVASCULAR RISK:

IMPLICATIONS FOR THE ADVANCED PRACTICE NURSE

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ABSTRACT

Elevated levels of C-reactive protein (CRP) are now known to correlate with an increased risk of cardiovascular disease (CVD) (Cushman, Arnold, Psaty, Manolio, Kuller, Burke, Polak, & Tracy, 2005; Khera, McGuire, Murphy, Stanek, Sandeep, Das, Vongatanasin, Wians, Grundy, & Lemos, 2005; Danik, Chasman, Cannon, Miller, Zee, Kozlowski, Kwiatkowski & Ridker, 2006). Per the Center for Disease Control and the American Heart Association “hs-CRP is the inflammatory marker of choice to assess cardiovascular risk” (www.circulationaha.org). Advance Practice Nurses (APNs) can use CRP as a tool to measure cardiovascular risk and determine appropriate treatment plans.
CHAPTER 1 INTRODUCTION

Elevated levels of C-reactive protein (CRP) are now known to correlate with an increased risk of cardiovascular disease (CVD) (Cushman, Arnold, Psaty, Manolio, Kuller, Burke, Polak, & Tracy, 2005; Khera, McGuire, Murphy, Stanek, Sandeep, Das, Vongatanasin, Wians, Grundy, & Lemos, 2005; Danik, Chasman, Cannon, Miller, Zee, Kozlowski, Kwiatkowski & Ridker, 2006). According to the Center for Disease Control and Prevention (CDC) and the American Heart Association (AHA), CRP is the marker of choice to measure CVD risk. CRP levels are stable over time, laboratory tests are inexpensive in cost, and sensitive in determining CRP. Nonetheless, high sensitivity CRP (hs-CRP) levels may fluctuate and be influenced by other variables independent of CVD. For example, CRP levels fluctuate and risk due to infections and inactivity (Ford, 2002). The degree of elevation that CRP levels may reach due to CVD risks and other variables remains unknown (Ridker, 2002; Pankow, Folsom, Cushman, Borecki, Hopkins, Eckfeldt, & Tracy, 2001). The CDC and AHA guidelines for measuring hs-CRP indicate that individuals with an hs-CRP level greater than 3.0 mg/L are at high risk for cardiovascular disease. In addition, it is also recommended by the CDC and AHA that an hs-CRP level greater than 10 mg/L should prompt the healthcare provider to search for causes of inflammation other than CVD. Because the potential fluctuations in hs-CRP levels due to causes other than CVD, it is often difficult for hs-CRP to be used as a direct predictor of CVD.

It is known, however, that the adoption of healthy lifestyles positively influences CRP levels and improves an individual’s CVD risk profile (Abramson & Vaccarino,
2002; Ford, 2002; Lakka, Lakka, Rankinen, Leon, Rao, Skinner, Wilmore, & Bouchard, 2005; Sundquist, Qvist, Johansson, & Sundquist, 2005; Li, Rana, Manson, Willett, Stampfer, Colditz, Rexrode, & Hu, 2006; Nicklas, Hsu, Brinkley, Church, Goodpaster, Kritchevsky & Pahor, 2008). In addition several current treatments for CVD have been shown to have a positive effect on CRP levels, such as treatment of diabetes, statin medications, and ARBs (Haffner et al, 2002; Beattie et al, 2003; Pfutzner et al, 2005; Ridker et al, 2008).

Advance Practice Nurses (APNs) and their patients can benefit from the data on CRP and its relationship to CVD. Healthy lifestyles and personal choices can positively impact CRP levels and subsequently reduce CVD risk. Reducing CRP can be a primary intervention to reduce CVD risk by educating patients on healthy lifestyles choices. Educating patients on negative behavioral choices, such as smoking, may also be beneficial. APNs may select therapies as a secondary prevention of CVD by choosing medications, such as ARBS or statins, which have been shown to decrease inflammation, CRP and CVD risk. Patients can be educated that CRP has a genetic component, but that they can positively affect their CVD risk by making healthy behavioral choices. APNs can empower their patients to choose a lifestyle that can benefit their heart, brain, and other vital organs, as well as their overall health. The investigations on CRP and other markers of inflammation have helped to advance the nonconventional notion of “adverse cardiovascular risk among seemingly healthy individuals” (Clearfield, 2005) which can lead to lives saved.
CHAPTER 2 CRP AS A MARKER OF ACUTE INFLAMMATION

Significance of the Problem

Cardiovascular disease (CVD) is the leading cause of mortality in the United States. (Ridker, 2007). All of the known risk factors for CVD, such as increase in age, gender, high fat diet, sedentary lifestyle and elevated BMI, do not explain all of the deaths or disabilities associated with CVD. According to Sundquist et al (2004), Americans’ body mass indexes (BMI) are continuing to increase at an alarming rate. The majority of vascular associated occurrences happen in individuals who do not have elevated cholesterol levels and one forth of all adverse cardiovascular related occurrences do not occur in individuals with traditional CVD risk factors (Ridker, 2007). Therefore, other factors are left to be determined to describe the disabling and fatal events associated with CVD. If other risk factors are discovered, then potential treatments may be developed to decrease the risk of developing CVD. Inflammation is believed to be a significant factor in CVD. Research examining potential inflammatory mediators of CVD include C-reactive protein (CRP), fibrinogen and white blood count(WBC) (Festa, D’Agostino, Howard, Mykanen, Tracy, & Haffner, 2000; Abramson & Vaccarino, 2002).

Definition of C-reactive Protein

CRP is an acute phase protein made in the liver (Ridker, 2003) that “promotes inflammation” (Ridker, 2007). CRP “is…a sensitive objective marker of inflammation, tissue damage, and infection” (Koenig et al, 1998). CRP increases in response to cytokines, such as interleukin 6 (Rosenson et al, 2003), and is believed to be a part of the immune system response (Ridker, 2003). CRP was discovered in 1930 by William
Tillett and Thomas Francis from the Rockefeller University while performing research involving individuals infected with pneumococcus. Further research was done in the 1940s by two researchers, Oswald Avery and Maclay McCarty, who described CRP as an “acute-phase reactant that increased in the serum of patients suffering from a spectrum of inflammatory stimuli, including myocarditis and inflammation associated with rheumatic fever” (Ridker, 2009). In the 1980s it was discovered that CRP was produced by the liver and increased in response to cytokines, such as interleukin-6 (IL-6) (Ridker, 2009).

What makes CRP a reliable predictor of CVD risk?

CRP remains constant over a period of time similar to an individual’s blood pressure or total cholesterol level (Danesh et al, 2004; Ridker, 2003; as cited by Ridker, Rafai, & Rose, 2002). This quality makes it a reliable marker for establishing CVD risk. There is a higher incidence of coronary artery disease (CAD) events with increased CRP” (Cushman et al, 2005). Measuring CRP utilizing hs-CRP is cost-effective and extremely sensitive in quantifying serum hs-CRP (as cited by Ridker, Rafai, & Rose, 2002).

CVD is believed to involve an inflammatory process that promotes atherosclerosis (Danesh, Wheeler, Hirschfield, Eda, Eiriksdottir, Rumley, Lowe, Pepys & Gudnason, 2004). Inflammation is a major component of atherosclerosis (Ridker, 2007). Atherosclerosis is initiated by damage “to the endothelial cells that line artery walls” (McCance & Heuther, 2002). Some of the potential causes of the injury to the endothelial wall include risk factors for CVD, such as positive history of smoking, hypertension, diabetes, hyperlipidemia, and elevated levels of CRP (McCance et al,
2002). When inflammation occurs in the vascular system, plaque may form that attracts cytokines like IL-6 or tumor necrosis factor (TNF) that causes an elevation in CRP. CRP is believed to advance atherosclerosis (Miliani et al, 2004). Interleukin-1 Beta (IL 1β) genes “regulate plasma CRP directly through CRP gene regulation and indirectly through the production of inflammatory mediators such as IL-6” (Enquobahrie et al, 2008).

IL-6 is one of the cytokines responsible for an increase in acute phase proteins, such as CRP. “Inflammation is a fundamental biological process underlying atherothrombosis, insulin resistance, and obesity that directly impacts CVD” (Ridker, 2007). Atherosclerosis is initiated by inflammation within the vessel and plaque develops and then adheres to the vessel. Damaged endothelial cells can “express various cellular adhesion molecules, E-selectin, cytokines, chemokines and growth factors” (Rosenson & Koeing, 2003). The damage “endothelial …cells produce IL-6 …and are expressed in atherosclerotic lesions” (Fernandez-Real & Ricart, 2003) As a result, CRP is produced. According to the guidelines issued by the CDC and AHA, hs-CRP levels less than 10 mg/L are indicative of CVD.

A study by Danesh et al (2004) involved 2,459 subjects to determine if CRP and other inflammatory markers were valid predictors of CHD. They concluded that the CRP level is a moderate predictor of CHD, and has long-term stability. In a review of literature on inflammatory markers of CAD, Rosenson et al (2003) supports CRP as a sensitive marker of inflammation and postulates that CRP may be utilized to monitor the progression of CAD.
Ridker et al (2002) compared CRP and LDL cholesterol levels in the prediction of first cardiovascular events. The study followed 27,939 healthy American women for approximately eight years for the occurrence of an adverse cardiovascular event, such as myocardial infarction, ischemic stroke or death. The women ages range from 45 to over 75 with the average age of 54.7. There was total of 571 adverse cardiovascular events that occurred. Seventy-seven percent of initial cardiovascular adverse events occurred in women with a LDL cholesterol less than 160mg/dL and 46% occurred in women with LDL cholesterol less than 130 mg per deciliter. In the study there was minimal correlation between LDL and CRP levels. Both markers identify individuals with an increased CVD risk. Possessing either an elevated level of CRP or LDL appears to identify groups with different cardiac risk profiles. This study supports CRP as adjunct for determining CVD risk in primary care settings.

The cause of elevated hs-CRP levels is multifactorial. Elevations in CRP levels may be caused by factors that are also known risk factors for CVD. CRP levels may be elevated by a positive history of smoking, elevated body mass index (BMI), elevated triglycerides, diabetes, hormone replacement therapy (Ridker, 2003), and metabolic syndrome (Lakka et al, 2005). Causes of decrease in CRP levels include decrease in BMI, dieting, physical activity and ceasing the utilization of cigarettes (Ridker, 2003). In an ten year observational study involving subjects 65 years or older by Cushman et al (2005), CRP was elevated in smokers, females, African Americans, individuals with elevated BMIs, individuals with decreased high density cholesterol (HDL), and individuals with a diagnoses of hypertension or diabetes. With an increase in BMI there is an increase in
adipocytes. As adipocytes increase this causes an increase in IL-6. This subsequently causes an elevation in CRP because IL 6 is one of the cytokines that causes an increase in acute phase reactants, such as CRP (Ford, 2002).

What factors confound CRP as a reliable predictor of CVD risk?

Factors not directly related to CVD that can result in elevations of CRP include acute infections, and traumatic events (Ridker, 2003). Chronic inflammatory states not directly related to CVD, other than the common link with inflammation states, that may increase CRP levels include: Alzheimer’s disease, and osteoarthritis (Nicklas et al, 2008); metabolic syndrome (Lakka et al, 2005); periodontitis and chronic bronchitis (Pankow et al, 2000). If CRP is a result of chronic inflammation unrelated to CVD, then per the CDC and the AHA guidelines, the hs-CRP level should be 10 mg/L or greater.

Gender, ethnicity, and genetic influences on CRP levels

There is evidence that CRP is influenced by genetics, ethnicity, gender and environment. Studies are ongoing in an attempt to delineate the factors that are influential. Khera, McGuire, Murphy, Stanek, Das, Vongpatanasin, Wians, Grundy and de Lemos (2005) conducted an observational study involving a population-based probability sample of subjects in a US city to investigate race and gender difference in CRP levels. The study involved 2,749 African American and Caucasians subjects between the ages of 30 and 65. The finding illustrated that in this sample, African Americans had higher hs-CRP levels than Caucasians. Women also had higher CRP levels than men. Two thirds of the African Americans in the study had an hs-CRP level greater than 3 mg/L. The study also found that an increase in BMI is associated with
higher hs-CRP levels in both genders and both ethnic groups studied. An increase in BMI was associated with a greater increase in CRP in women than in men in this study. The median CRP levels were 30% higher in African Americans than in Caucasians. The findings affirm that the female gender and the African American race are associated with higher hs-CRP levels, at least in the population studied.

There is a lack of research on the genetic component of CRP. There is some evidence that shows that CRP is influenced by both environment and genetics (Ridker, 2007). There are many single nucleotide polymorphisms that can potentially influence CRP levels to decrease or increase (Miller, Zee, Danik, Kozlowski, Chasman, Lazarus, Cook, Ridker & Kwiatkowski, 2005; Danik, Chasman, Cannon, Miller, Zee, Kozlowski, Kwiatkowski & Ridker, 2006).

Paik et al (2007) conducted a study involving 677 healthy Asian adult men older than forty to determine the relationship among “inflammation-related genes and CVD risk…focusing on IL-6/CRP SNPs and CRP concentration” (Paik et al, 2007). Exclusion criteria included: orthopedic injuries, diagnosis of diabetes, and hepatic or renal dysfunction. Three genotypes were identified for IL-6: GG, GC, GG. The GG genotype had the highest insulin levels as well as the highest CRP levels. The GC genotype had the lowest insulin levels as well as the lowest CRP levels. Three genotypes were identified for CRP: GA, CT, and AG. There was no significant difference between the insulin levels or CRP levels for either genotype identified. The findings illustrated that “CRP concentration and insulin resistance appeared to be more influenced by IL-6 gene than CRP SNPs” (Panik et al, 2007).
A cross sectional study by Pankow et al (2000) examined the influence of genetics on hs-CRP levels in Caucasian families involving parents, children and their spouses. The subjects were genotyped and hs-CRP levels were determined. The average age was 52.5 years with a range of 25 to 93. Approximately 50% of the subjects had a history of smoking, and 13% had significant CHD. The median hs-CRP level was 1.7mg/L at the initiation of the study. The study looked at various sociodemographic factors, such as age and education; lifestyle factors such as cigarette smoking and alcohol use; obesity and presence of diabetes. Subjects’ lifestyle factors, such as smoking or no physical activity, contributed to 13% variability between individuals’ traits. This provides evidence that negative environmental factors may have more of an effect on CRP levels than genetics. In the study the correlation between married couples’ CRP levels was not significant. This provides support for a greater genetic influence on CRP levels compared to environmental influences. There was a moderate and positive correlation for hs-CRP for first degree relatives providing evidence of a genetic component of CRP levels. The findings of this study support a genetic as well as an environmental influence on markers of inflammations.

A study by Enquobahrie, Rick, Williams, Williams, Gross, Lewis, Schwartz & Siscovick, (2008) researched CRP to determine if Interleukin-1 Beta (IL1-β) genetic variation is connected to levels of CRP and also studied obesity to determine if and how obesity may affect the relationship between CRP and IL1-β. The studied involved 3,289 adults, men and women, age 18-30, that were participating in the Coronary Artery Risk Development in Young Adults (CARDIA) study. The participants were followed for
fifteen years. The subjects were genotyped and genotyping of 10 selected single nucleotide polymorphisms (SNP) were conducted. At the conclusion of the study, black males’ average CRP was 3.1 mg/L, black females’ average CRP was 4.8 mg/L, white males’ average CRP was 2.0 mg/L and white females’ average CRP was 2.8 mg/L. Women had higher CRP levels than men and blacks had higher CRP levels than whites consisted with previous studies. Blacks also had higher BMIs than white. Blacks had nine different halotypes and white had five. Halotype 1 was most common among the entire study population and among white. Halotype 4 was most common among blacks. There was not a significant change in CRP levels associated with any specific halotypes, but there seem to be correlation between obesity and CRP levels. The findings of the study propose that CRP levels may be partially determined or influenced by the IL 1β genetic variation and that CRP levels may be negatively influenced by obesity in certain populations. The results of the study supports weight lost as a means to improve lifestyle, decrease CRP levels, and also improve CVD risk. In summary, the evidence is mounting regarding the influence of genetics on CRP levels. There is a better understanding that CRP levels may have a genetic component, such as SNP II-1β genetic variations, but it seems that environmental factors and behavioral choices also influence CRP levels.

Guidelines for measuring risks of CVD using CRP

Guidelines from the Center for Disease Control and Prevention and the American Heart Association were developed in 2003 to guide how hs-CRP should be consistently integrated within healthcare practice (www.circulationaha.org). Hs-CRP is the “inflammatory marker of choice to assess cardiovascular risk” (www.circulationaha.org).
The guidelines suggest that elevated hs-CRP may be useful in helping individuals make healthy lifestyle changes to positively affect their cardiovascular health. In individuals who have been diagnosed with acute coronary syndromes (ACS), the hs-CRP may be used to guide subsequent interventions. If the provider chooses to measure the CRP level, then two hs-CRP levels should be done, one fasting and the other one randomly, when the person is not experiencing an acute infection. The two hs-CRP levels should be averaged. The average of the two hs-CRP should be utilized to guide care.

The guidelines endorse the following average hs-CRP values that correspond to a relative risk category for CVD risk: low risk is less than 1 mg/L, average risk is 1.0 to 3.0 mg/L and high risk is greater than 3.0 mg/L. Hs-CRP is categorized as an independent marker of risk instead of a risk factor of CVD. The guidelines do not recommend that all adults are “screened for hs-CRP for purposes of cardiovascular risk assessment” (www.circulationaha.org). The guidelines suggest that individuals with hs-CRP greater than 10mg/L should be assessed for other sources of inflammation that are not related to CVD. Although there is currently insufficient evidence to support that CRP be measured on a routine basis in the primary care setting, there is evidence that supports checking CRP in individuals who meet certain criteria that increases their chance of having an elevated CRP level (www.circulationaha.org). As previously discussed, CRP levels have shown to be elevated in individuals with an elevated BMI, individuals with an insulin insensitivity, African Americans (Cushman et al, 2005) and smokers (Ridker, 2003). In addition, the JUPITER study (Ridker, P., Danielson, E., Fonseca, F., Genest, J., Gotto, A., Kastelein, J., Koenig, W., Libby, P., Lorenzatti, A., MacFadyen, J., Nordestgaard, B.,
Shepherd, J., Willerson, J., & Glynn, R. 2008), which will be described in detail below, provides evidence that individuals who do not meet the current LDL criteria for statin therapy, but have elevated CRP levels, in fact, benefit from statin therapy. The JUPITER study is important because, for the first time, it identifies that targeting inflammation is beneficial in reducing CVD risk even when LDL levels are not elevated.
CHAPTER 3 PREVENTION AND TREATMENTS THAT TARGET CRP

Statins and CRP

Statins are traditional therapy for hyperlipidemia. Although, new research is discovering additional benefits of statins beyond improving the lipid profile. Statins have been found to be effective at reducing inflammation which is believed to be a significant factor in atherosclerosis.

The Justification for the Use of Statins in Prevention: an Intervention Trial

Evaluating Rosuvastatin (JUPITER)  

Ridker et al (2008) conducted a randomized, double-blind, placebo controlled trial involving 17,802 individuals in 26 countries that lasted for 1.9 years. The purpose of the trial was to determine if Rosuvastatin would lower the cardiovascular risk in individuals with a LDL less than 130 mg/dL and an hs-CRP greater than or equal to 2.0 mg/L. Current guidelines recommend treatment with a statin when individuals have an increased cardiovascular risk and a LDL greater than 130mg/dL. The inclusion criteria included: men 50 years or older, women 60 years or older, no history of cardiovascular disease, LDL less than 130mg/dL, and an hs-CRP 2.0 mg/L or greater. The subjects consisted of 38% women, 25% were African American or Hispanic, and 41% had metabolic syndrome. At the initiation of the study, the median LDL was 108 mg/dL and the median hs-CRP was 4.2 mg/L in the participants receiving Rosuvastatin and 4.3 mg/L in the control group. The exclusion criteria included: current or previous use of a HMG Co-reductase inhibitors (statins), current use of postmenopausal hormone-replacement therapy, hepatic dysfunction, elevate creatinine kinase, diabetes, uncontrolled hypertension, cancer within five years of the study, uncontrolled
hypothyroidism, history of alcohol or drug abuse, history of inflammatory diseases such as lupus, and current treatment with immunosuppressant therapy. The primary endpoint of the study was “first occurrence of a major cardiovascular event” (Ridker et al, 2008). The finding of the study was that Rosuvastatin drastically decreased the incidence of major cardiovascular events. At the endpoint of the study, 142 adverse cardiovascular events had occurred in the treatment group and 251 adverse cardiovascular events had occurred in the control group. There were fewer patients that experienced myocardial infarctions or cerebrovascular events while taking Rosuvastatin. The primary endpoint occurred after 1.9 years at the occurrence of the first major cardiovascular event. “The number…need to be treated… for 2 years to prevent the occurrence of one adverse cardiac event is 95” (Ridker et al, 2008). The study provides support that Rosuvastatin may provide cardiovascular protection for individuals who would not routinely meet the recommended guidelines for treatment with a statin. The main weakness of the study was the brief treatment interval. The study provides strong support that individuals with elevated hs-CRP may benefit from a statin because it decreases inflammation while subsequently reducing the hs-CRP and decreasing CVD risk. The JUPITER trial is a pivotal trial that demonstrates the anti-inflammatory effects of a statins. Importantly, the results of this trial indicate that treating “inflammation”, even in the face of normal traditional risk factors, prevents first vascular events.

Plenge, Hernandez, Weil, Poirier, Grunwald, Marcovina, & Eckel (2002) conducted a crossover, double-blind study consisting of 40 subjects, age 25 to 75, to determine how quickly Simvastatin can lower CRP levels within individuals and to
determine how rapidly CRP levels change after cessation of the statin therapy. The study also compared CRP against LDL changes with statin therapy. The inclusion criteria included having an elevated LDL level. Exclusion criteria included diagnoses of inflammatory diseases, renal or hepatic disease, diagnoses of anemia, leukocytosis, thrombocytosis or diabetes and current therapy with corticosteroids. The trial was conducted in two phases; both phases consisted of fourteen days. In the first phase one group received Simvastatin 40 mg or a placebo. In the second phase the group that received the placebo received the treatment and the group that received the treatment received the placebo. As illustrated in previous studies, women had higher CRP levels prior to the initiation of the study. The average hs-CRP for women was 2.8mg/L and 1.1 mg/L for men. At the conclusion of the study the average CRP in the subjects receiving Simvastatin decreased from 2.55 mg/L to 1.60mg/L and in the placebo group the CRP increased from 2.0 mg/L to 2.2 mg/L illustrating an inverse relationship which was statistically significant. The fibrinogen levels were also measured and did not show a change during the study period which may be due to the brief length of the study. The LDL in the placebo group increased from approximately 20 points from 160 mg/dL to 180 mg/dL while the treatment group’s LDL decreased from approximately 60 points from 160 mg/dL to 100 mg/dL. Although the LDL and CRP decreased in the treatment group, there was no correlation between the LDL and CRP changes which is significant because it illustrates that CRP reduction is independent and not associated with LDL reduction. Changes in the treatment group, illustrates that Simvastatin can make a significant difference in a short period of time. The author suggested that treatment with
Simvastatin may be useful as an early intervention to individuals who have suffered an adverse cardiac event, such as an acute coronary syndrome.

**Anti-hypertensive Treatment and CRP**

Anti-hypertensive medications are beneficial for reducing blood pressure as well as decreasing inflammation and subsequently CRP levels. Ridker et al (2006) compared therapies with valsartan and valsartan/HCTZ to determine which therapy has the best blood pressure reduction effect, and also to determine which therapy decreases hs-CRP. “Elevated levels of CRP are associated with increased risk of developing hypertension” (Ridker et al, 2006), as well as increasing the risk of adverse cardiovascular events. The study involved 1668 subjects, male and female, who either received monotherapy with valsartan for six weeks or therapy with valsartan/HCTZ for six weeks. The subjects were between the ages of 18 and 75 and all had Stage II hypertension. The exclusion criteria include: systolic blood pressure greater than 185 mm Hg; diastolic blood pressure greater than 109; diagnosis of a chronic inflammatory disease; history of myocardial infarction, CVA or unstable angina; and therapy within three months of the trial with aldosterone receptor antagonists, angiotensin receptors blocks (ARB), angiotensin-converting enzyme inhibitors (ACEI) or thiazide diuretics. At six weeks, there was a greater reduction in systolic as well as diastolic blood pressure for the patients receiving the combination therapy. There was a consistent decrease for all subjects, regardless of gender, race or age, in hs-CRP for the group receiving the monotherapy. This was not seen in the group receiving the combination therapy. Because valsartan resulted in a decrease in hs-CRP but the valsartan/HCTZ did not exhibit the same effect, this “suggests
that the observed effect is unlikely to be attributable to the blood pressure reduction” (Ridker et al, 2006), and gives credence that valsartan and other ARBs have anti-inflammatory properties and subsequently decrease hs-CRP levels. The combination therapy decreased blood pressure the most, but it failed to show the same effect in hs-CRP.

Jenkins, Keevil, Hutchinson, & Brooks (2002) conducted a study with 333 patients undergoing elective cardiac catheterization to determine the effect of beta-blockers on CRP levels. All patients had either stable angina or coronary artery disease (CAD). Exclusion criteria included: positive history of valve disorders, previous coronary artery bypass surgery, compromised immune system, cancer, autoimmune diseases, renal disease and individuals with contraindications to beta-blockers. Patients’ CRP levels were measured and compared with their medication regiments. The patients on beta-blockers were on the medications for an average of 14 months. Patients receiving beta-blockers had the lowest average CRP of 1.8 mg/L when compared to other medications regiments such as statins or nitrates. In the study beta-blockers illustrated a 31% reduction in CRP levels. This study provides evidence that beta-blocker decreases CRP and may be beneficial to patients with a history of hypertension and elevated risks for inflammation, such as smoking.

Treatment of Diabetes and CRP

“Patients with type 2 diabetes mellitus exhibit an increased propensity to develop extensive arteriosclerosis” (Pfutzner et al, 2005). Festa, D’Agostino, Howard, Mykkanen, Tracy and Haffner (2000) conducted a multicenter, population based study that
researched the association between insulin resistance and inflammation. The hypothesis was that insulin insensitivity may be associated with inflammation in nondiabetic individuals and that hyperinsulinemia may be associated with circulating CRP levels. The study involved 1,008 subjects between the ages of 40-69 without cardiovascular disease. The findings of the studies illustrated that people that are type II diabetics have higher levels of inflammatory markers and present with a higher incidence of atherosclerosis. The studied showed an increase in CRP levels that corresponded with the number of metabolic disorders, such as dyslipidemia and insulin resistance. The findings also illustrated that in healthy nondiabetic subjects, CRP was independently related to insulin sensitivity. The findings provide support of the relationship between diabetes and CAD. The findings also provide support of treatment of diabetes as a method to reduce inflammation and subsequently CRP levels.

Rosiglitizone (RSG), a treatment for type 2 diabetes mellitus, is effective at managing hyperglycemia as well as decreasing CRP. Haffner, Greenberg, Weston, Chen, Williams, & Freed (2002) conducted a 26 week, randomized, double-blind, placebo-controlled study with 357 subjects with type 2 diabetes mellitus to determine if the thiazolidinediones could decrease markers that are shown to increase the chances of adverse cardiovascular events. They also researched whether rosiglitazone can change the “serum concentrations of CRP, IL-6, and matrix metalloproteinases (MMP)” (Haffner et al, 2002). CRP and IL-6 are “markers of inflammation” and MMP is a marker for atherosclerotic “plaque stability” (Haffner et al, 2002). The study consisted of three groups: a placebo group, a group that received RSG 4 mg daily and a group that received
RSG 8 mg daily. Serum levels of the biomarkers were measured at baseline and after 26 weeks of therapy. The majority of the subjects was male with an overall average age of 60 and had BMI’s greater than 30 kg/m². The average length of a diagnosis of diabetes was over four years and the preponderance of the participants had received some type of pharmacological therapy for treatment of their diabetes. Most of the subjects had HbA1C levels that were greater than eight and fasting glucose levels was greater than 200mg/dl. Approximately half of the subjects had a history of CVD and hypertension. All subjects with a history of pharmacological treatment for their diabetes stopped their medications at least four weeks prior to the initiation of the study. At the conclusion of the trial the group receiving the higher dose of RSG had the greatest weight gain of 3.5kg and both groups receiving RSG demonstrated significant changes in their CRP levels. However, there was not a dose response noted with two different regiments of RSG. This indicates that higher doses may be indicated for the treatment of diabetes, but not necessarily for the reduction of CRP. WBCs were also decreased with RSG use. The small change in IL-6 levels was similar between the placebo group and the RSG groups. It is presumed that the change in IL-6 may be undetectable between the RSG and placebo group because of “the observed weight decrease in the placebo group and the weight gain in the RSG group” (Haffner et al, 2002). Both RSG groups had changes in MMP-9 when compared with the placebo group. There was a 12.4% difference between placebo and the low dose RSG and a 23.4% difference between placebo and the high dose RSG group. As seen in previous studies, (Ridker, 2002; Plenge et al, 2002) the changes in CRP did not correlate with the changes in LDL levels. “The data support the potential beneficial effects of
insulin-sensitizing interventions such as use of thiazolidinediones on levels of markers for cardiovascular risk” (Haffner et al, 2002).

Pfutzner, Marx, Lubben, Langenfeld, Walcher, Konrad and Forst (2005) conducted a six month randomized study to determine if pioglitazone could reduce inflammation and the progression of atherosclerosis. The study consisted of 173 subjects with a diagnosis of type 2 diabetes for over seven years. Over 50% of the subjects were male, and the average HbA1c was greater than seven. To determine the effectiveness of pioglitazone the following markers were assessed: HbA1c, fasting glucose, lipids, hs-CRP, fibrinogen, MMP-9, and carotid intima-thickness (IMT). There were two treatment groups with one group receiving pioglitazone 45 mg/day and the other group receiving glimepiride 1 to 6 mg/day. The exclusion criteria included: hepatic or renal disease, congested heart failure (CHF), positive smoking history and no carotid artery disease. Biomarkers were measured at the initiation of the study and upon conclusion. The pioglitazone treatment group had a greater decrease in fasting glucose levels that subjects treated with glimepiride. The pioglitazone treatment group experienced a considerable increase in HDL levels and decrease in tryiglycerides and the glimepiride group had a considerable decrease in total cholesterol. At the conclusion of the study the subjects who received pioglitazone had a major reduction in CRP levels and MMP-9, but this was not seen in the group who received glimepiride. Neither therapy had a major impact on fibrinogen levels. Also there was noteworthy regression of carotid IMT in subjects who received pioglitazone. The positive changes experienced are not correlated with “improvement in long-term glucose control” (Pfutzner et al, 2005). At the conclusion of the study the
average HbA1C was still elevated above six in both groups although both groups showed a reduction. The findings provide “evidence of an anti-inflammatory and potential antiatherogenic effect of pioglitazone that is indicated by improvements in … cardiovascular risk markers and carotid IMT, independent of an improvement in long-term glycemic control” (Pfutzner et al, 2005). Patients with type 2 diabetes mellitus and other risk factors for CVD disease may benefit from treatment with pioglitazone to reduce hyperglycemia as well as inflammation.

Influence of Healthy Lifestyles on CRP

Ford (2002) examines the effect of leisure time physical activity on CRP levels using a multistage, stratified sampling design. The study consisted of 13,748 Americans twenty years or older that was a representative sample of the US population. Most of the following variables were examined based upon predetermined relationship with CRP levels: age, sex, ethnicity, education, working status, smoking status, hypertension, BMI, waist-to-hip ratio, total cholesterol, LDL, high-density cholesterol (HDL), triglyceride, aspirin use, alcohol consumption, and fruit and vegetable intake. Participants rated their leisure activity level as none, light, moderate, and vigorous. The results of the study show that the CRP levels range from less than 3.0 mg/dl to 252.0 mg/dl (less than 3.0mg/dl to 198.0 mg/dl for men and less than 3.0 to 252.0 mg/dl for women). In this study an elevated CRP was defined as 4.4mg/dl or higher for men and 7.0mg/dl or higher for women which is higher than the parameters specified by the AHA and CDC (www.circulationaha.org). The findings illustrated an inverse relationship between physical activity, age, cigarette use, and diagnosis of hypertension. The CRP levels were
inversely related to the amount of exercise. Less of the vigorously active subjects had elevated CRP levels. Eight percent of the vigorously active subjects had elevated CRP levels, 13% of moderate active subjects, 17% of the lightly active subjects, and 21% of sedentary subjects had elevated CRP levels. Therefore, this study supports that exercise decreases inflammation as determined by elevated CRP levels. There is a dose effect with the amount of exercise performed. This may be a motivator for Americans to become physically active.

Milani, Lavie & Mehra (2004) conducted a nonrandomized three-month study with 277 subjects with coronary heart disease. All of the subjects have experienced an adverse cardiac event, such as coronary artery bypass or myocardial infarction. The purpose of the study was to determine if cardiac rehabilitation and exercising training can reduce hs-CRP without statin therapy or weight reduction. Not only did the cardiac rehabilitation and exercise training decrease hs-CRP, but it also caused a decrease in cardiac risk factors, such as lipid levels, weight and exercise capacity. Subjects received individual and group counseling on dietary management, formal exercise instruction, attended regular scheduled group exercise classes, and were encouraged to exercise independently. Individuals characterized as overweight or obese were provided weight management classes. Classes were provided to all on hypertension, smoking cessation and diabetes management. There was a 41% median reduction in hs-CRP. When comparing the exercise group who received a statin to the group who did not use a statin, there was a similar reduction in hs-CRP. Subjects on statins had a 42% reduction in hs-CRP compared to a 38% decrease in hs-CRP in individuals did not take a statin. When
comparing the subjects who gained or lost weight, both groups experienced an average
decrease in hs-CRP. The subjects who lost weight experienced an average decrease in hs-
CRP by 31%. The subjects who gained weight had an average decrease in hs-CRP by
42%. The study provides support that CRP can be decreased significantly by exercise
solely. The findings illustrate that healthy lifestyles changes, such as exercise, can
decrease inflammation as and subsequently CRP levels. Lifestyles changes can
significantly improve an individual’s cardiac profile even after an adverse event such as
myocardial infarction.

Abramson and Vaccarino (2002) examined the affect of physical activity on the
markers of inflammation, such as CRP, fibrinogen, and white blood count. The aim of
the study was to determine if physical activity decreased markers of inflammation. The
study involved 3638 healthy American men and women 40 years or older who had
previously participated in the Third National Health and Nutrition Examination Survey.
Exclusion criteria included being less than 40 years of age, and possessing chronic illness
such as rheumatoid arthritis, asthma or cancer. The findings of the study show that CRP
levels are inversely related to physical activity level. Individuals with a high activity level
had lowers markers of inflammation with respect to WBC, CRP and Fibrinogen.
Conversely individuals with a low activity level had the highest inflammatory markers
with respect to WBC, CRP, and fibrinogen.

In the study conducted in the United States and Canada by Lakka et al (2005)
studied healthy families and researched how CRP levels changed with exercise. The
study consisted of 652 Caucasian and Black families consisting of parents and children.
The subjects participated in a 20 week uniformed exercise program. Approximately 33% of the subjects were black and 45% were men. Approximately 19% of the subjects use hormones and 12.9% were current smokers. The average BMI for all subjects was 26.6 kilograms per meter square. The average systolic blood pressure for all was 118.6 mmHg and the average diastolic blood pressure was 68.3. The purpose of the study was to research how exercise influences risk factors for Type 2 diabetes and CVD in black and white families. The parents were 65 years or older and the children were 17 years or older. The inclusion criteria included sedentary lifestyle. The exclusion criteria included possessing a chronic disease or prescribed medication that may alter lab results. Baseline CRP was taken prior to initiating an exercise program and upon completion of the program. Elevated CRP levels were seen overweight and obese individuals, and individuals with elevated glucose, triglycerides, LDL cholesterol or diastolic blood pressure. CRP levels also were higher in individuals with a decreased HDL and elevated systolic blood pressure. Overall, there was a small change in CRP levels, but the greatest decrease in CRP was witnessed in individuals, regardless of age or sex, who have an elevated CRP greater than 3 mg/L. One of the most significant changes for all subjects with a CRP greater than 3.0mg/L was the reduction of the CRP to 1.34mg/L providing support that short-term exercise programs can positively affect CRP levels.
CHAPTER 4 FINDINGS SIGNIFICANT TO ADVANCED PRACTICE NURSES

The data presented on CRP is valuable in primary care settings because it provides evidence of cardiovascular risk stratification beyond that of traditional cardiac risk factors. Rosenson et al (2003) postulated that CRP levels can help to identify individuals at risk of developing CVD, it can help monitor the progression of CVD and that in the future it may be utilized as a target of therapy. The data presented on CRP also can be utilized in scenarios to determine therapy when patients who have several cardiac risk factors, but are not at the traditional threshold for initiating statin therapy. CRP levels may warrant a more aggressive treatment and the initiation of medications, such as statins. “The addition of CRP to standard cholesterol evaluation may thus provide a simple and inexpensive method to improve global risk prediction and compliance with preventative approaches” (Ridker, 2003). Some of the most important information presented in this paper, and perhaps not as widely acknowledged in the practice setting, is that healthy lifestyles can positively influence CRP levels. Physical activity has been shown to decrease CVD risk, and it also decreases blood pressure, lipid levels, and helps to prevent type II diabetes mellitus (Sundquist et al, 2004). Not only is obesity a risk factor for CVD, but it also can influence CRP levels negatively. Therefore, Advanced Practice Nurses (APNs) as well as nurses throughout the spectrum of care should encourage their patients to adopt healthy lifestyles to decrease their chance of experiencing an adverse cardiovascular event and to improve their quality of life. Information on CRP and CVD can be used to reinforce the maintenance of healthy
lifestyles also. “Long-term stability of CRP values are similar to both BP and total serum cholesterol...making CRP have the potential to be used in the long-term prediction of CHD” (Danesh, 2004). The relationship for inflammation, CRP and CVD may lead to new therapies to decrease inflammation and CRP, and subsequently decrease CVD risks.

Traditionally, in addition to prescribing healthy lifestyles choices, practitioners target elevated LDL levels, hypertension, and hyperglycemia. In the last decade, well-designed clinical studies have provided that these conventional therapies also decrease systemic inflammation, as measured by CRP. Until the recent JUPITER study, there was not strong evidence that lowering inflammation (CRP), in the absence of elevation in LDL, was beneficial. The results of the JUPITER study are important because they illustrate that statin therapy may be beneficial to individuals who are not routinely treated with statins. Statins have shown to have an affinity for reducing inflammation and cardiac risk factors. Statins are beneficial because not only do they lower CRP levels, but they also lower LDL levels which is also important to an individual’s cardiovascular health.

Traditional treatments for hypertension and hyperglycemia are now known to be effective at reducing CRP. The ARBs have been shown to reduce blood pressure as well as inflammation. This is beneficial because it can reduce two CVD risks factors, CRP and blood pressure. Thiazolidinediones, pioglitazone and rosiglitazone, are effective at managing hyperglycemia as well as reducing inflammation. This is also beneficial because it also reduces two CVD risk factors, inflammation and hyperglycemia. These
treatments may have a significant affect on APNs when determining the most appropriate therapies for an individual with multiple risk factors for CVD.

Evidence based guidelines have now been established to instruct providers on how to utilize CRP levels. It has been established that hs-CRP levels less than 10 mg/L correlate with CVD while hs-CRP levels greater than 10 mg/L may be signs of infection. Therefore, providers in primary care settings can utilize this knowledge to help patients’ assess their CVD risk, but they can also use it as a justification to search for other sources of infection.

CRP is the inflammatory marker of choice according to the CDC and AHA. CRP is an “independent predictor of future CVD events and a strong predictor of future CVD risks in patients with established CHD with or without previous myocardial infarctions” (as quoted by Clearfield, 2005). Due to its stability over time and the availability of high sensitivity assays (Ridker, 2003), CRP is an exceptional choice to help predict CVD risks in patients in a variety of healthcare settings.

Research continues to elucidate how inflammation is relevant to CVD. There is now evidence to help patients understand that controlling their diabetes can increase their cardiovascular health by reducing inflammation and decreasing their chances of experiencing an adverse cardiovascular event. It is now known that there are differences in CRP based on gender and ethnicity. CRP is elevated in females when compared to males, and blacks when compared to whites (Khera et al, 2005). It is now known that genetics as well as environment influences CRP (Pankow et al, 2000), and that obesity and elevated BMI can increase CRP (Enquobahrie et al, 2008). It is now known that there
is minimal correlation between LDL cholesterol and CRP levels (Plenge et al, 2002; Rikder, 2003). Each identifies a different cardiovascular profile. This evidence can be utilized to help APNs and other healthcare providers target therapies that can decrease inflammation (CRP). The evidence helps establish evidenced-based practice and tailor therapies based upon a patient’s unique attributes and characteristics. CRP is an emerging biomarker for CVD.
AHA/CDC Guidelines on hs-CRP

Population Science

1. The entire adult population should not be screened for hs-CRP for purposes of cardiovascular risk assessment. (Class III, Level of Evidence C)

Clinical Practice

1. Measurement of hs-CRP is an independent marker of risk and, in those judged at intermediate risk by global risk assessment (10 to 20% risk of CHD per 10 years), at the discretion of the physician, may help direct further evaluation and therapy in the primary prevention of CVD. The benefits of such therapy based on this strategy remain uncertain. (Class IIa, Level of evidence B)

2. Measurement of hs-CRP is an independent marker of risk and may be used at the discretion of the physician as part of a global coronary risk assessment in adults without known CVD. The benefits of this strategy remain uncertain. (Level of Evidence C)

3. hs-CRP levels may be useful in motivating patients to improve lifestyle behaviors. The benefits of this strategy remain uncertain. (Class IIb, Level of Evidence C)

4. Patients with persistently unexplained, marked elevation of hs-CRP (>10mg/L) after repeated testing should be evaluated for noncardiovascular etiologies. (Class IIa, Level of Evidence B)

5. Other inflammatory markers (cytokines, other acute-phase reactants) should not be measured for the determination of coronary risk in addition to hs-CRP. (Class III, Level of Evidence C)

6. In patients with stable coronary disease or acute coronary syndromes, hs-CRP measurement may be useful as an independent marker of prognosis for recurrent events, including death, MI, and restenosis after PCI. The benefits of therapy based on this strategy remain uncertain (Level of evidence B).

7. Application of secondary prevention measures should not depend on hs-CRP determination (Level of evidence A).

8. Application of management guidelines for acute coronary syndromes should not be dependent on hs-CRP levels (Level of evidence A).

9. Serial testing on hs-CRP should not be used to monitor effects of treatment (Level of evidence C).

Laboratory Science

1. Of current inflammatory markers identified, hs-CRP has the analyte and assay characteristics most conducive to use in practice. (Level of Evidence B)

2. Measurement of markers should be done twice (averaging results), optimally two weeks apart, fasting or nonfasting in metabolically stable patients. If hs-CRP level is >10mg/L, test should be repeated and patient examined for sources of infection or inflammation. (Level of Evidence B).

3. hs-CRP levels, using standardized assays, categorize patients as follows (relative risk category and average hs-CRP level): Low <1mg/L, Average 1.0 to 3.0 mg/L, and High >3.0mg/L. (Class IIa, Level of Evidence B)

4. hs-CRP results should be expressed as mg/L only. (Level of evidence C)
REFERENCES


