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The predictive value of C-Reactive Protein in relation to the development of cardiovascular disease

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Introduction

The American Heart Association estimates that by 2035 over 130 million or 45.1 percent of the American population is projected to have some form of cardiovascular disease, defined as coronary heart disease, stable/unstable angina, heart failure and stroke. It is expected that the total cost of treatment for patients with cardiovascular disease will reach 1.1 trillion by 2035 accordingly. Approximately 17.9 million deaths that were reported in 2016 were related to cardiovascular disease based on the World Health Organization statistics. The American College of Cardiology and American Heart Association suggest that primary prevention is accredited to early identification of modifiable and nonmodifiable risk factors therefore, early recognition is pivotal in decreasing all-cause morbidity and mortality of cardiovascular disease. Modifiable risks factors such as diet, activity level, and smoking are often utilized as risk stratification for cardiovascular risk; however, lipid profiles such as non-high-density lipoprotein (HDL) and low-density lipoprotein (LDL) remain at the forefront as a positive predictor of cardiovascular risk. While it has been established that the proportion of HDL to LDL play an integral role in the progression of cardiovascular disease, it also is thought that inflammation contributes in the progression of coronary artery disease. The Centers for Disease Control and Prevention and the American Heart Association concluded that it is reasonable to measure C-reactive protein (CRP) a sensitive circulating biomarker of inflammation as an adjunct to the measurement of established risk factors in order to better assess the risk of coronary heart disease.[1]

According to the study conducted by Dr. Edward T.H. Yeh Department of Cardiology, University of Texas, approximately half of patients with an initial cardiovascular event did not have any known risk factors.[2] Currently medical professionals screen patients for risk factors to identify opportunities for prevention, therefore, a novel risk factor such as C-reactive protein

may help identify patients at risk for cardiovascular disease (CVD). Current evidence suggests that inflammatory biomarkers such as CRP have been shown to be just as effective in predictive value for CVD in comparison to low-density lipoprotein.[2]

Background

CRP was originally discovered by Tillet and Francis in 1930. It reacted to C polysaccharide of pneumococcus from which the name was derived. The formation of atherosclerotic plaque is a very complex process that involves inflammatory mediators, lipid formation and platelet dysfunction. C- reactive protein is an inflammatory mediator produced by the liver that is elevated in the acute phase of inflammation. As a proinflammatory bio marker, CRP is thought to increase the uptake of LDL by macrophages and enhance the local expression of inflammatory mediators. While lipid deposition is the foundation in which atherogenic plaque is formed, inflammatory mediators such as CRP have a distinct role in amplifying the atherogenic cascade by activating interleukin-1(IL-1), interleukin-6 (IL-6) and tumor necrosis factor alpha (TNFa), which contributes to the inflammatory damage that occurs to blood vessels. CRP has been shown to inhibit nitric oxide production in the vessels, which can lead to vasoconstriction and decreased compliance within vessels that may be occluded by plaque. It is important to note that CRP exists in two distinct forms that are associated with very different pathological processes. Pentameric CRP or (pCRP) does not induce thrombosis but does contribute to plaque instability by increasing endothelial cell adhesion expression. Pentameric CRP does have a less significant role in the amplification of inflammatory mediators in comparison to monomeric CRP (mCRP). While monomeric CRP or mCRP does promote thrombosis by amplification of the inflammatory cascade and is involved in the progression of

cardiovascular disease. Therefore, monomeric CRP is involved with the large inflammatory cascade that directly contributes to myocardial damage and infarct size.[3]

According to the article by Badimon, CRP Antithrombosis and Angiogenesis suggested that increased levels of CRP are strongly predictive for the thrombotic complications of atherosclerosis, and CRP may have a role in the risk stratification of patients with established cardiovascular disease. In subjects with intermediate risk, incorporation of CRP to a model assessment of cardiovascular risk improves the prognostic power for myocardial infarction presentation and could help prevent one additional cardiovascular related death in 10 years with 400-500 patients screened. In patients with a previous history of CVD and in asymptomatic subjects, high sensitivity-CRP (hs-CRP) was demonstrated to be a moderate predictor of cardiovascular disease. In patients with stable and unstable angina elevated CRP levels are predictive of future coronary events. Elevated CRP levels predicted heart failure and cardiovascular mortality the year after the cardiovascular event. In patients with non-ST elevation myocardial infarction in- hospital mortality was higher in patients with a CRP greater than 10mg/L.[3]

Discussion

In the Reykjavik Study, initiated in 1967 as a prospective study of cardiovascular disease, took a total of 8888 men and 9681 women without a history of cardiovascular disease born between 1907 and 1934, and chronicled the subject's medical history over the course of decades until 1995. The study demonstrated that the decade to decade consistency for proinflammatory markers such as CRP, and Erythrocyte Sedimentation Rate (ESR) as well as the platelet adhesion protein known as von Willebrand factor yield similar predictive values in comparison to blood pressure and total serum cholesterol concentration. This suggests that inflammatory markers

may provide reliable data points in the long-term prediction of coronary heart disease.[1] This study further demonstrates that inflammatory biomarkers may play a role in the prediction of cardiovascular disease.

The meta-analysis conducted by Li-ping He, Xin-yi Tang assessing early C- reactive protein in the prediction of long-term outcomes after acute coronary syndromes, evaluated the relation between early elevations of CRP after an acute coronary event and risk of adverse outcomes. In this study which included 20 longitudinal studies comprising 2789 cases from a population of 17,422 patients concluded that patients with higher CRP levels >10.0 (mg/l) after acute coronary syndrome (ACS) were associated with 1.40-fold to 2.18-fold higher risk of adverse outcomes as compared with patients with lower CRP levels.[4] The resulting studies demonstrate the correlation of elevated CRP levels and associated cardiovascular related events.

The Women's Health study, a prospective case control study concluded that those with the highest CRP levels had double the risk for developing cardiovascular disease. Of the patients that subsequently developed a cardiovascular related event, nearly half of the subjects had LDL levels < 130mg/dl, therefore suggesting that hs-CRP had a role in risk stratification. This study further illustrated the correlation of higher hs-CRP levels in postmenopausal women who subsequently had cardiovascular related events, compared to those that did not have elevated hs-CRP levels. The study noted that of the 12 markers of inflammation that were highly correlated to major adverse cardiovascular complications, hs-CRP was shown to be the most powerful predictor of risk in the univariate analysis. Each of the markers of inflammation significantly improved the usefulness of predicting risk, but models using both hs-CRP and lipid profiles were better predictors of cardiovascular risk than were models that used only total cholesterol alone. This data does support the notion that the incorporation of hs-CRP to the standard lipid screening

may assist in the identification of patients at high risk for cardiovascular related events and improve the primary prevention of interventions such as statin therapy.[5]

C- Reactive Protein in clinical practice

The incorporation of CRP in clinical practice may assist clinicians in the management of patients with LDL values <160mg/dl that would normally be treated as moderate risk patients. This could lead to more effective management and better outcomes as compared to the traditional lipid measuring analysis. Lifestyle and dietary modifications may be an area that the clinician may want to expound upon as CRP has also been shown to be elevated in patients that were sleep restricted. The study conducted by Van Leeuwen et al. comparing patients that habitually underwent sleep restriction of five days, produced elevated levels of IL-1, IL-6, IL-17 proinflammatory cytokines which are associated with increased expression of CRP. This study correlates the link between sleep restriction and greater risk for CVD. As the increasing number of patients with busy lifestyles continues, many patients in today's society are constantly being subjected to a sleep deprived state, having the science to educate patients on the risk of sleep deprivation and the association with cardiovascular disease may benefit patients at risk and potentially benefit from early intervention.[6]

The Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT) trial demonstrated similar findings to those of the Reversal of Atherosclerosis with Aggressive Lipid Therapy trial (REVERSAL) which established regression of atherosclerotic plaque when both LDL and CRP were lowered , therefore postulating that there may be a decrease in cardiovascular events if stain therapy is based not only LDL measures but CRP values as well.

In addition, hs-CRP has been shown to predict vascular risk in patients undergoing percutaneous coronary interventions and coronary bypass graft surgery. In patients with elevated hs-CRP that had acute coronary syndromes were shown to have a poorer prognosis.[7] The studies bring forth new questions with regards to identifying other inflammatory markers as a means for determining diagnostic and therapeutic adjuncts. While CRP may be strongly correlated to cardiovascular disease, the biomarker may also be elevated in other inflammatory conditions which would make the use of CRP as a screening tool more sensitive and less specific for cardiovascular disease. Other limitations to note are many of the studies were conducted in predominately homogenous patient populations, thereby providing very little insight on weather CRP is a reliable predictor of CVD in minority groups. Other studies found that CRP may not be a reliable predictor of cardiovascular disease in patients greater than 65 years of age in comparison to traditional risk factors.[8,9]

Conclusion

CRP may be used as an adjunctive test to correlate cardiovascular risk in patients that are suspected of having cardiovascular disease. Screening for lifestyle modifications will be supportive in the prognosis and future outcomes in patients with cardiovascular disease. The standard of care could be potentially influenced as preventative measures may be taken in patients with low to moderate risk factors that demonstrate elevated CRP levels. Further evidence is warranted in the development of screenings that carry a greater magnitude of scientific backing demonstrating hs-CRP as potentially being used for risk stratification in patients suspected of cardiovascular disease. Currently, the standard of care revolves around risk modification and lipid management, however CRP may also serve as a diagnostic tool used in the prevention of CVD resulting in better management of patients that are at risk for

cardiovascular complications. The data compiled to date is compelling suggesting a greater degree of research is necessary to establish screenings using hs-CRP as a mainstay of preventative screening in comparison to non-HDL or other traditional risk factors such as tobacco use and hypertension. Therefore, future areas of investigations are warranted in the discovery of new inflammatory mediators linked to cardiovascular disease.

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