Editorial

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The Role and Clinical Significance of High-Sensitivity C-Reactive Protein in Cardiovascular Disease

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Atherosclerosis, the leading cause of cardiovascular disease, is characterized by chronic inflammation in the artery wall. It has been considered for decades that this disease is associated with hypercholesterolemia and the accumulation of macrophage-derived foamy cells in the arterial wall. While inflammation is involved in initiation, progression, and complication of the atherosclerotic process, the exact mechanisms underlying this inflammatory process remains unclear as yet.

C-reactive protein (CRP) is a homopentameric acute-phase protein produced by the liver and binds specifically to phosphorylcholine in a Ca^{2+}-dependent manner. Its levels rise dramatically during inflammation that occurs in the body. This increment of CRP is due to a rise in the plasma concentration of interleukin-6 (IL-6), produced predominantly by macrophages[1] and adipocytes.[2] During the acute phase response, CRP levels increased rapidly within 2 hours of acute insult, rise above normal limits within 6 hours, and peak at 48 hours. With resolution of the acute phase response, CRP declines with a half-life of 18 hours. CRP can rise up to 50000-fold in acute inflammation, such as during infection. Its level is mainly determined by its rate of production because of its constant half-life. One exception is that the CRP elevations in the absence of clinically significant inflammation can occur in renal failure.

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C-reactive protein is a general nonspecific marker for inflammation and infection, so it can be used as a very rough proxy for the risk of cardiovascular disease. Since many factors can be associated with an elevated CRP level, this is not a very specific prognostic indicator. Nevertheless, a CRP level above 2.4 mg/L has been associated with a doubled risk of a coronary event compared to CRP levels below 1 mg/L.[1] Nowadays, we consider CRP as an important risk marker for cardiovascular disease in addition to being a prototypical marker of underlying inflammation. Patients with high CRP concentrations are more likely to develop stroke, myocardial infarction, and significant peripheral vascular disease. Moreover, a study showed that trans-fat consumption is related to high blood levels of CRP.[3] However, studies did not show always consistent regarding the clinical significance of CRP on cardiovascular disease. The Reykjavik Study indicated that CRP may be a moderate risk factor for cardiovascular disease,[4] and there were several studies showing a modest to minimal association between CRP and future cardiovascular events.[5][6] This is partially dependent upon the individual's status such as age, sex, number of risk factors, and metabolic conditions.

It is a significant issue to clarify whether CRP is a simple bystander or an active participant in atherogenesis. Zacho et al.[7] compared people with various genetic CRP variants. Those with a high CRP due to genetic variation had no increased risk of cardiovascular disease as compared to those with a normal or low CRP. Although some controversies exist, several studies have demonstrated that CRP is not only an inflammatory marker, but also an inflammatory mediator acting on vascular cells. A recent study showing the novel evidence for the pro-inflammatory action of CRP involved in atherogenesis reported that CRP is able to stimulate IL-6 production and inhibit PPARγ expression in vascular smooth muscle cells via MyD88-independent toll-like receptor-4 signaling pathway. Another study revealed a role for CRP in promoting differentiation of human monocytes toward a proinflammatory M1 phenotype.[8]

It is intriguing as to whether the inhibition of CRP increase can be a safe and effective therapy for myocardial and cerebral infarc-

tion, but this has been demonstrated in an animal study.[9] Statins have been proven to reduce levels of CRP; this finding is based on the JUPITER study that tested that statin administration was beneficial to subjects with elevated CRP levels, who did not have hyperlipidemia.[10] In the JUPITER study, a total of 17802 healthy individuals with low density lipoprotein-cholesterol level less than 130 mg per deciliter and elevated CRP levels of ≥2.0 mg per liter, investigators showed that 20 mg rosuvastatin significantly reduced the primary end point - a composite of nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina, revascularization, and confirmed death from cardiovascular causes - by 44% compared with individuals treated with placebo. However, the amount of the absolute benefit and cost-effectiveness were very small. Moreover, a subsequent trial failed to prove that CRP was useful for determining the clinical benefit of statins, despite of 40 mg simvastatin for 5.5 years.[11]

Despite this evidence regarding the role of CRP in atherosclerotic vascular diseases, we still cannot use the CPR test for routine clinical practice to measure the current status of cardiovascular risk. Because there are a variety of conditions that can increase CRP production, an elevated CRP level alone itself does not diagnose or predict a specific cardiovascular disease. An elevated CRP level can support only for the presence of an inflammatory disease, regardless of its mechanism. This is one of reasons why the American Heart Association (AHA) limited the clinical utility of CRP in real world clinical practice. The AHA has stated that high sensitivity C-reactive protein (hs-CRP) may be useful in evaluating those persons at moderate risk for heart disease and determine whether or not more intensive treatment is warranted. Those at high risk should be treated aggressively regardless of their hs-CRP level. The AHA does not recommend hs-CRP testing as routine screening for people who are not at high risk for heart disease.

In this issue of the Journal, Jeong et al.[12] performed a novel study to test the relationship between the baseline hs-CRP level and 12-month clinical outcomes in 8174 patients with acute myocardial infarction (AMI) undergoing percutaneous coronary intervention (PCI) according to their body mass index status. Higher baseline hs-CRP level (≥4.08 mg/dL) in overweight/obese AMI patients showed significant association with 12-month all-cause mortality independent of other prognostic markers, but individuals with normal- or under-weight did not have a significant association of serum hs-CRP level with 12-month mortality, though this cohort consisted of only patients with AMI. Baseline hs-CRP in patients with AMI might be associated with vascular inflammation with atherosclerosis, myocardial necrosis, and remote inflammation related to underlying risk factors. All of these factors can negatively impact on future cardiovascular outcomes, but mechanisms of different factors can be quite diverse. Inflammation by myocardial necrosis is usually transient but vascular inflammation with atherosclerosis and remote inflammation due to underlying risk factors can be persistent and more longstanding. Of these, vascular inflammation associated with AMI itself could be reduced with standard medical therapy following PCI. However, inflammation related to innate risk factors, such as obesity, is hard to control with only standard medical therapy. More aggressive lifestyle modification would be required with standard medical therapy. All of these efforts might be very helpful to prevent future cardiovascular events by controlling the source of chronic inflammation.

The result of this study may further suggest that a CRP test result can be a surrogate prognostic marker for the patients with definitive risk factors associated with chronic inflammation such as obesity or diabetes. In overweight/obese AMI patients undergoing PCI, if the residual risks related to inflammation persist, I would like to prescribe the highest tolerable statin as recommended by the EAS/ESC guideline 2011 in addition to lifestyle modification.[13] Those patients with normal- or under-weight also may have residual risks, but the degree of chronic inflammation and its clinical significance is not clear yet in this population. One possible explanation is that atherosclerotic progress is associated with multifactorial causes. There are several ways of research to clarify the mechanism. One is to develop more specific serologic markers, such as lipoprotein-associated phospholipase A_2, and another is molecular imaging to visualize the vulnerable lesion for proper evaluation of residual cardiovascular risks. But, this result from KAMIR study shows that measurement of CRP can be a very helpful and a cost-effective method to predict future cardiovascular outcome in a specific group of patients.

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