

THE CLINICAL UTILITY OF CRP

Atherosclerosis, a product of numerous risk factors, is now also seen as a disorder of chronic inflammation. C-reactive protein (CRP) is one of several biological markers of inflammation. CRP derives its name from its ability to bind to the C-polysaccharide of the pneumococcal cell wall. CRP is released from the liver in situations of acute inflammation (along with fibrinogen and serum amyloid A) in response to a host of cytokines – primarily Interleukin-1 beta (IL-1 beta) and Interleukin-6 (IL-6) and tissue necrosis factor alpha (TNF-alpha). These inflammatory cytokines are expressed “upstream” from the liver by the heart, adipocytes, macrophages and the vessel wall. (Figure 1)

CRP has been found to be both a marker and a mediator of atherosclerotic vascular disease and may exacerbate the proinflammatory effects of several inflammatory mediators, including endotoxin and enhances the cellular uptake of LDL. Multiple epidemiological studies have associated CRP with myocardial infarction, stroke, peripheral vascular disease and sudden cardiac death. Elevated CRP in patient’s with unstable angina has been associated with an increased risk of future ischemic events and the need for future cardiac revascularization. Since CRP levels are temporally very stable and are not influenced by circadian variation or food intake, fasting blood samples for CRP levels are not necessary. High sensitivity CRP levels (hs-CRP) are ten times more sensitive than regular CRP levels. Hs-CRP levels of less than 1, 1 to 3, and >3 mg/L correlate to low, moderate or high risk patient groups, respectively (Figure 2). Although women taking hormone replacement therapy (HRT) will have higher levels of CRP, several large studies, including the Women’s Health Study, suggest that there is little clinical need to have separate cut-off points for CRP based on gender or HRT use. Several parameters decrease CRP levels (Figure 3). While LDL cholesterol has been a focus of current ATP-III guidelines, elevated CRP levels seem to closely identify patient subsets that may have increased risk of future cardiac and vascular events. In the CARE lipid trial of secondary prevention, Pravastatin use in those with elevated CRP levels resulted in a nearly 55% benefit compared with a 30% benefit for those with low CRP levels and Pravastatin therapy. In the AFCAPS-TexCAPS primary prevention study, Lovastatin was effective in patients with elevated CRP levels even when LDL levels were below the current ATP-III guidelines. The Women’s Health Study demonstrated that CRP levels may help further stratify high risk individuals with those at highest risk showing high CRP and high LDL levels. Of greater interest is the fact that survival was worse in those individuals with an elevated CRP and low LDL compared with elevated LDL and low CRP (Figure 4). While CRP has focused interest on the concept of dynamic inflammation as an important aspect of vascular disease, many questions remain regarding the clinical utility of this serum marker, and currently “ATP III does not recommend routine measurement of inflammatory markers for the purpose of modifying LDL cholesterol goals in primary prevention”.⁴

SUMMARY

- It would appear that CRP may be useful in helping to direct not only the initiation of therapy, (i.e., individuals with LDL levels between 130-160 mg%, and few or no additional risk factors, an elevated CRP may suggest the need to initiate statin therapy - Figure 5) – or to embrace an even more aggressive goal with dyslipidemic therapy. It is also pertinent to note that in the Heart Protection Study, clinical benefit was seen in patients even with LDL levels less than 100 mg/dl perhaps suggesting the importance of other parameters that may exacerbate vascular disease such, as inflammation.
- While CRP and knowledge of inflammatory status may be useful in directing therapy, as yet there are no definitive levels of CRP that define risk in the setting of acute ischemia.
- The prevalence of CRP elevation is a function of the clinical syndrome (Figure 6). While only half of patients with coronary artery disease have hypercholesterolemia, only half of patients who suffer a myocardial infarction in the absence of a prodrome of unstable angina will have an elevated CRP. In addition, 35% of patients who present with unstable angina will have normal CRP levels.
- There is currently no data from prospective studies that demonstrate that lowering CRP will reduce cardiovascular event rates or that levels of CRP objectively measure the severity of vascular disease. There is also no evidence to suggest that CRP should be used to recommend performing non-invasive or invasive studies in totally asymptomatic individuals. Prospective randomized clinical studies are currently underway to address these questions and until additional information is obtained, CRP appears to hold promise as a useful tool in helping to further stratify patients and perhaps more aggressively pursue lipid management goals in specified patient subsets.

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