High-Sensitivity C-Reactive Protein and Cardiovascular Disease

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About a half of all myocardial infarctions (MI) occur in individuals without overt hyperlipidemia. More than three quarters of all cardiovascular events occurs among those with low-density lipoprotein (LDL) cholesterol levels below 160 mg/dL, and just less than half occurred among those with LDL cholesterol levels below 130 mg/dL.[1] About 20% of all coronary events occur in the absence of any major risk factor.[2] In one recent analysis patients with CHD, 15% of the men and 19% of the women had no evidence of any major risk factor, and more than 50% had only 1 of these factors.[3]

In background of this some novel risk factors, including high sensitivity C-reactive protein (hsCRP), lipoprotein(a), homocysteine, fibrinogen, D-dimer, tissue plasminogen activator, and plasminogen activator inhibitor-1 antigen has attracted the attention in recent years. Among these hsCRP is the most promising biomarker in terms of clinical utility.[4]

hsCRP emerged as the most powerful single predictor of cardiovascular risk including CHD death, nonfatal MI, stroke, coronary revascularization & outcome of peripheral arterial disease.[5] Inflammation is characteristic in all phases of atherothrosclerosis and provides a link between early fatty streak formation up to plaque rupture leading to occlusion and infarction.[6] Proinflammatory cytokines such as interleukin-l(IL-1) and tumor necrosis factor(TNF) potentiate the expression of adhesion molecules on vascular endothelial cells, leading to the recruitment of leucocytes to the arterial wall,. IL-1 & TNF also activate chemokines that promote migration of monocytes into the subendothelial space. Mononuclear cells release growth factors that stimulate the proliferation of smooth muscle cells and lead to plaque progression. Mediators such as CD40 ligand induce tissue factor expression and promote thrombus formation. Primary proinflammatory cytokines also stimulate the expression of interleukin-6, which create enhancement of inflammatory response, which leads to the production of CRP.

What is CRP

CRP is a member of the pentraxin family of innate immune response proteins (composed of 5 23-kd subunits), synthesized by the liver in response to interleukin-6. Recent evidence suggests that CRP is also produced by smooth muscle cells of coronary arteries (particularly diseased vessels).[7] It has been reported that levels of CRP in atherosclerotic plaque were 7-and 10-fold higher than that in the liver and normal blood vessels.[8] CRP influence vascular vulnerability (in vitro) by enhanced expression of endothelial cell surface adhesion molecules,[9] monocyte chemoattractant protein-*(1)* endothelin[10] and endothelial plasminogen activator inhibitor[11] reduced endothelial nitric oxide activity;[10] and increased LDL uptake by macrophages[12] Recent data also indicate that expression of human CRP enhances intravascular thrombosis in endothelial disruption.[13]

Serum hsCRP concentrations are lower than the tissue CRP concentrations (which promote atherogenic responses) Serum hsCRP levels less than 1 mg/L labeled as low, 1 to 3 mg/L labeled as intermediate, and greater than 3 mg/L labeled as high-risk. CRP at the cellular level usually ranges from 5 to 900 mg/L during inflammatory responses. On the other hand CRP concentrations as low as 5 mg/L have been implicated to decrease nitric oxide production.[10] One study suggests that low concentrations of hsCRP (<0.5 mg/L) are almost never associated with the future vascular event whereas concentrations greater than 10 mg/L

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represent very high risk.[14] Cut off value for clinically significant' circulatory level is >1 mg/L.

To reduce misclassification in clinical practice, hsCRP should be measured during acute stress, and both are recommended to be measured twice (preferably 2 weeks apart) because hsCRP levels have stability similar to that of LDLC on a month-to-month, year-to-year, and even decade-to-decade basis as has been observed in multiple prior studies.[15]

hsCRP and Cardiovascular Risk

hsCRP predicts future cardiovascular risk in a wide variety of populations, including healthy individuals patients with acute coronary syndromes, stable angina , after MI, after percutaneous coronary intervention (PCI) and patients with the metabolic syndrome, diabetes, or renal disease.

hsCRP and Subclinical Atherosclerosis: Epidemiologic studies on general populations have found inconsistent associations between hsCRP and evidence of subclinical atherosclerosis such as carotid intimal-medial thickness (IMT) and coronary calcification as measured by electron beam computed tomography (EBCT). In a subset of Framingham Study, the top quartile of hsCRP was associated with relative risk (RR) of carotid stenosis (e"25%) of 3.90 (95% CI, 2.44-6.44) among women and 1.62 (95% CI, 1.12-2.36) among men *(16)* . hsCRP level also correlated positively with the extent of coronary artery calcification in healthy participants evaluated with EBCT *(73).* Another study reported that persons with hsCRP level in the top tertile of the sample distribution were twice as likely to have moderate or severe carotid plaques than were persons in the bottom tertile (>2.77 vs <1.11 mg/L: RR, 2.0; 95% CI, 1.3-3.0) after adjustment for BMI and other covariates *(17).* Autopsy studies have shown that elevated hsCRP is associated with increased macrophage density in atherosclerotic plaque, a higher prevalence of cap thinning, and increased risk of plaque erosions and rupture.[18]

In a 10-year follow-up study on elderly participants who had no history of stroke or atrial fibrillation at baseline, elevated hsCRP was predictive of ischemic stroke, independent of atherosclerosis severity.[19] During follow-up of the same cohort, there was also a stronger relation between hsCRP and subsequent MI among individuals with evidence of subclinical disease than among those without such evidence.[20]

Acute coronary syndromes: A study reported that patients presenting with unstable angina and elevated plasma levels of hsCRP and serum amyloid A suffered higher adverse outcomes than did patients without the same, even in the absence of troponin elevation.[21] TIMI investigators reported that the increased cardiac risk associated with high hsCRP levels may be evident as early as 14 days after presentation with an acute coronary syndrome.[22] CAPTURE trial of abciximab in unstable angina poulations found that, hsCRP predicted risk of mortality or MI at 6 months[23] and at 4 years.[24] FRISC trial (on low-molecular-weight heparin) reported the risk associated with elevated hsCRP levels at the time of the index event (unstable angina in 61% and MI in 39% of participants) continued to increase during a 3-year follow-up.[25]

In the TIMI, CAPTURE, and FRISC studies, the predictive value of hsCRP was shown to be independent of, and additive to, troponin. An approach using hsCRP, troponin I, and B-type natriuretic peptide has been shown to improve risk prediction in patients with acute coronary syndromes.[6] In patients of the TIMI trial (categorized on the basis of the number of elevated biomarkers at presentation), there was nearly doubled 30-day mortality risk for each additional biomarker elevation. Similar relations also existed for the endpoints of MI and congestive heart failure, and for the composite of the 3 outcomes, at 30 days and at 10 months.

Stroke: Recent reports suggest that hsCRP may be useful in predicting risk of subsequent cardiovascular events among persons with ischemic stroke. hsCRP levels were measured in ischemic stroke patients within 24 hours after onset. Compared with those in the bottom hsCRP quartile (<5 mg/L), individuals with an hsCRP level in the top quartile (>33 mg/L) and middle two quartiles (5-33 mg/L) had RRs of 4.04 and 1.37 respectively, of a future cardiovascular event in 2 years of follow-up.[27]

After percutaneous coronary intervention: It has been reported that hsCRP strongly predicted early

complications (30-day risk of death or MI) after PCI in patients with a high percentage of use of stents and glycoprotein IIb/IIIa inhibitors; with the RR was 3.68 for the highest (>10 mg/L) vs lowest (<1.6 mg/L) quartile comparison. The risk associated with elevated CRP was independent of, but additive to, the ACC/AHA lesion score.[28] It was reported in a study (on patients of stable angina having received elective angioplasty) that hsCRP level (>3 mg/L vs <3 mg/L) was found to be a strong independent predictor of adverse coronary outcomes (death, MI, urgent revascularization, or admission for unstable angina) with a RR of 2.5.[29] hsCRP was reported to be a better predictor than diabetes, hypertension, and ACC/AHA lesion class,. In another report, patients undergoing elective or urgent angioplasty were followed for up to 14 months.In multivariate analyses, elevated CRP level (>3 vs <3 mg/L) was an independent predictor of death or nonfatal MI (RR, 3.6).[29] Nearly similar results came out of a 1-year follow-up of patients with stable angina who had undergone coronary stenting; Elevated. CRP levels (>5vs<5 mg/L) were associated with a 1.8-fold increase in rate of death or MI but baseline hsCRP levels did not correlate with restenosis.[30]

Another follow up study of patients (who had undergone stenting of the culprit lesion) compared individuals with hsCRP levels of e"10 mg/L with CRP levels d"10 mg/L. Higher CRP was implicated in RR of 4.2 for in-hospital death and a RR of 4.07 for death within 20 months.[31]

It was reported that preoperative elevated hsCRP (>3vs<3 mg/L) was associated with an increased risk of recurrent ischemia at 1 to 6 years after coronary artery bypass grafting[32] hsCRP is also predictive of cardiovascular events in symptomatic patients of angiographically determined significant stenosis who are treated medically Absolute risk of death or MI found in patients with the lowest CAD scores (those with normal angiograms) and the highest hsCRP levels exceeded the risk for patients with highest CAD scores with the lowest hsCRP levels despite a higher prevalence of traditional coronary risk factors.[33]

Inflammation appears to be systemic rather than localized in patients with acute coronary syndromes but the precise source of CRP elevations remains unclear.[34] It has been documented that hsCRP levels did not change after PTCA in patients with stable or unstable angina with normal preprocedural CRP levels but did increase after PTCA in patients with unstable angina and elevated hsCRP levels at baseline.[35] Plaque rupture may not be the source of elevated hsCRP levels in unstable angina, but elevated hsCRP in this setting may be suggestive of hyper-responsiveness of the inflammatory system to smaller stimuli. As sirolimus and similar coatings present an antiproliferative, anti-inflammatory surface interface with the endothelium. These coated stents are likely to decrease event rates among individuals with elevated levels of hsCRP. hsCRP may be an important factor in the decision to use the drug eluting stents in certain patients, thereby potentially reducing the economic burden associated with widespread nonselective use of drug eluting stents. On the contrary if inflammatory activity is widespread and not limited to the lesion site drug eluting stents may not decrease future events.

Chronic phase after Myocardial Infarction: It has been reported in the CARE study that, patients with elevated hsCRP levels at 3 to 20 months after the MI were at higher risk of recurrent events during the 5-year follow-up period.[36] Another study of patients with premature MI also found hsCRP to be a strong predictor of future cardiac death. The 10-year RR of cardiac mortality doubled with increasing CRP quartiles. Patients in the top quartile had 6 times the risk of cardiac death than did patients in the bottom quartile(adjusting age, left ventricular ejection fraction, serum cholesterol, fibrinogen, smoking, and hypertension).[37] Another study found that, hsCRP levels measured 2 months after the index MI significantly predicted the risk of recurrent coronary events but the association lost the significant after adjustment for ejection fraction and presence of pulmonary oedema.[38]

In another study, hsCRP levels were measured in stable angina patients with or without exercise induced ischemia Individuals with levels of 3.8 mg/L or above were far more likely to have exercise-induced ischemia (RR, 4.2; 95% CI, 1.6-11.0).[39] Thresholds used to define an abnormal or elevated CRP level among patients with documented coronary disease range from 3 mg/L

to 5 mg/L.[28,29] CAPTURE investigators found that a threshold of 10 mg/L maximized the predictive value of CRP in patients with unstable angina.[23] Lowest distribution has been among healthy individuals, an intermediate range in stable CAD, and the highest range in acute coronary syndromes.[40]

Practical Considerations of hsCRP

hsCRP Assays: Traditionally CRP has been used to monitor active infection & inflmmmation related to musculoskeletal system. These assays are automated, reproducible, have a lower detection limit of 3 to 8 mg/L and is not sensitive enough to detect the lower levels for prediction of cardiovascular risk. To improve the sensitivity of CRP assays, the useful approach has been to amplify the light-scattering properties of the antigen-antibody complex by covalently coupling latex particles to a specific antibody. Most of the nearly 30 types of hsCRP assays, presently used employ this commercially available approach.[41] Commonly used methods achieved sensitivities of less than or equal to 0.3 mg/L and had analytic variabilities of less than 10% (reproducibility >90%).[42]

Biologic Properties of CRP: hsCRP exhibits a relatively low range of variability in the same stable patients. In a study it was reported that , two separate measurements of hsCRP in the same individual 90 days apart classified of 90% of values in the same or immediately adjacent biomarker tertile.[43] The CARE trial, reported moderate positive correlation (r= 0.6) between two hsCRP measurements 5 years apart.[44]

If a value less than 10 mg/L is obtained, it is believed that a single hsCRP assessment is sufficient. The CDC and AHA recommend two hsCRP measurements taken 2 or more weeks apart, and the mean value is used to predict vascular risk.[4] hsCRP levels may increase upto 100-fold or more in response to acute infections or trauma, Levels above 10 mg/L should be ignored initially and the test repeated after stabilization. If elevation persists, then connective tissue disease, inflammatory bowel disease, or endocarditis should be excluded (particularly with elevated erythrocyte sedimentation rate). It has been reported, that individuals with persistent & significant elevations of hsCRP appear to have exceptionally high coronary risk.[14] In clinical studies, fewer than 2% of hsCRP values exceeds15 mg/L, and persistent elevations are rare. hsCRP levels are not influenced by food intake or circadian rhythm.[43] Owing to its pentraxin structure, hsCRP has a long plasma half-life (18 to 20 hours), Measurements can be made accurately from fresh or frozen blood (serum/plasma) without the need for special collection procedures. *(41).* CRP has been shown to be stable at 4°C for 60 days,[45] at 70°C for longer than 20 years,[46] and in liquid nitrogen for an indefinite period.[47] hsCRP levels have demonstrated specificity for vascular events and not predictive of cancer.[48] A population-based cohort study of women (>65 years) reported that an elevated CRP level strongly predicted cardiovascular mortality (CRP >3 vs<3 mg/L: adjusted RR, 8.0) but was unrelated to mortality from noncardiovascular causes.[49]

Population Distribution of hsCRP: Ranges of less than 1, 1 to 3, and greater 3 mg/L, correspond to tertiles of the CRP distribution in healthy adults, which classifiy of individuals into low-, moderate-, and high-risk groups for primary cardiovascular prevention,[4,50] Individuals with the lowest hsCRP levels (<0.5 mg/L) are at very low cardiovascular risk, whereas those with long-term marked elevations of hsCRP (>10mg/L) are at very high risk.[14]

Genetic influence: Different studies suggest that CRP concentrations are in part genetically determined & heritability of serum CRP level is approximately 40% to 50%.[51]

Sex: Circulating hsCRP concentrations, measured by high-sensitivity assays, appears comparable among men and women with the 50th percentile for both sexes being approximately 1.5 mg/L.[47] hsCRP levels are higher in women who use oral HRT which may be partly responsible for the increased risk of thrombotic events associated with oral HRT use.[52] Selective estrogen receptor modulators do not raise hsCRP levels[53] nor do transvaginal or transdermal estrogens.[54]

Age: Most studies report a modest relation between age and serum CRP concentrations.[41,47] Reported median hsCRP concentrations for individuals aged 45 to 54, 55 to 64, 65 to 74, and 75 years or older were 1.31, 1.89, 1.99, and 1.52 mg/L, respectively.[41]

Race/ethnicity. There was no reported significant differences in the distributions of hsCRP levels among European-American, African-American, Mexican-American men. and Japanese men.[55] In contrast, hsCRP concentrations are reportedly higher in Mexican-American women than in European-American women.[53] African-American women (compared to whites) had higher hsCRP levels and Asian-American women had lower level of hsCRP (compared to Hispanics).[57]

Therapeutic Interventions

It has not yet been conclusively proved that that lowering hsCRP levels leads to reduction in future cardiovascular events. many behavioral and pharmacologic interventions known to reduce the risk of clinical cardiovascular events have been linked to lower hsCRP levels. The goal of cardiovascular screening programs is the identification of high-risk individuals who can be targeted for weight loss,smoking cessation, increased physical activity, blood pressure control, and, where necessary, pharmacologic therapy. A patient's compliance with recommended interventions depends at least in part on his or her perception of absolute disease risk. Because the addition of hsCRP to lipid evaluation improves the prediction tool, hsCRP screening may be useful for this reason alone.

Pharmacologic Interventions: Several pharmacologic agents with demonstrated ability to reduce hsCRP levels.

1. Lipid-lowering agents: Lipid-modulating medications reported to affect hsCRP levels favorably include HMGCoA reductase inhibitors (statins), fibrates, and niacin. Statins are by far the most effective.

1.1. Statins: Cardiovascular benefits of statins extend beyond LDL cholesterol reduction. Benifits of statin therapy comes sooner than expected (even when LDL cholesterol has not started to reduce). Patients taking statins have a better prognosis than patients not taking the same even when LDL cholesterol levels are matched.Statins reduce ambulatory ischemia and symptomatic angina, events not generally explained by LDL reduction alone;. Statins also reduce risk of stroke although LDL cholesterol is not a major risk factor.,The CARE trial.first reported the hsCRP lowering ability of statins (pravastatin) because of its possible anti-inflammatory effects in addition of lipid-lowering.[36,44] Confirmatory work showed that effect of statins on hsCRP was a consistent and important class effect. A meta-analytic review of the effects of statins on CRP, fibrinogen, homocysteine, oxidised LDL cholesterol, tissue plasminogen activator, plasminogen activator inhibitor, and platelet aggregation concluded that, among these, only hsCRP appears to be reduced by statins.[58] All statins (pravastatin, lovastatin, cerivastatin, simvastatin, and atorvastatin) have shown to reduce median CRP levels by 15% to 25% as early as 6 weeks after initiation of therapy in different subsets of CAD patients.[58,59] This reduction in CRP levels (and improving lipid profiles) is augmented by the addition of ezetimibe, (a cholesterol absorption inhibitor not affecting triglycerides and fat-soluble vitamins.[60] Though ezetimibe alone had no reported effect on hsCRP. Magnitude of LDL cholesterol reduction due to statin therapy is minimally correlated with the magnitude of hsCRP reduction.[58] It has been reported that the cardiovascular risk reduction attributable to statin therapy may be most marked in those having elevated hsCRP levels at baseline. In the CARE trial, recurrent events prevented by pravastatin was 54% among persons with elevated hsCRP levels but only 25% among persons with lower hsCRP levels, though baseline lipid profile were nearly identical in both groups.[44] In a primary prevention trial, lovastatin therapy was associated with a 42% reduction in first cardiovascular events among participants with LDL cholesterol levels <149 mg/dL but hsCRP levels >1.6 mg/L.[61] It has been reported that high hsCRP confers a dramatic increase in cardiovascular risk even in the absence of elevated LDL cholesterol. The randomized JUPITER trial investigating the effect of rosuvastatin vs. placebo on men and women with LDL cholesterol levels below 130 mg/dL but hsCRP levels above 2 mg/L in 4 year follow up to see the effect on first vascular events was stopped prematurely because of significant reduction in cardiovascular morbidity.[71] The JUPITER trial also provided the proof of relative benefit of hsCRP reduction as compared with LDL cholesterol reduction.[72]

1.2. Fibrates: Small trials have shown that fibrates may also decrease plasma concentrations of hsCRP

and other inflammatory markers in dyslipidemic patients[62,63] CRP-lowering ability of fenofibrate (200 mg/d) was compared with that of atorvastatin (10 mg/d) and fenofibrate treatment was found to be more effective,[64] In a double-blind trial fenofibrate and simvastatin (20 mg/d) found to be equally effective.[64] Gemfibrozil, was shown to lower cardiovascular event rates without a significant reduction in LDL cholesterol.[65]

1.3. Niacin: It has been shown that combination of niacin and lovastatin (1000 & 20-mg respectively), reduced median hsCRP levels in dyslipidemic patients by 4% at 8 weeks and doubling the dose reduced hsCRP by 24% at one year (P . .01)[66] In another double-blind randomized trial on type 2 diabetic patients niacin (at doses of 1000 or 1500 mg/d,) reduced median hsCRP levels by 11%, and 20% compared to placebo.[67]

2. Aspirin and other antiplatelet agents: A large primary prevention trial reported that the risk of future MI was reduced 56% by aspirin (325 mg on alternate days) in those with baseline CRP levels in the highest quartile and reduction was only 14% among those in the lowest quartile of CRP.This observation might suggest that aspirin may prevent ischemic events through anti-inflammatory as well as antiplatelet effects.[68] Published data indicate that the effects of clopidogrel and abciximab may be strongest in patients with elevated CRP levels before PCI.[28,69] In contrast, ticlopidine conferred a significant reduction in subsequent cardiovascular events after ischemic stroke with admission hsCRP levels in the bottom 2 tertiles.. Nonsignificant excess risk was evident among those in the highest CRP tertile.[27] Whether aspirin or other antiplatelet agents can lower CRP directly is uncertain. One trial found that six weeks of aspirin therapy (300 mg/d) significantly reduced CRP levels in patients with stable angina.[70]

Clinical Recommendations

Persons for whom National Cholesterol Education Program guidelines call for therapeutic intervention (based on serum LDL) an elevated hsCRP level should provide a strong impetus to improve compliance with diet and pharmacologic therapy. Whether or not patients with normal levels of LDL cholesterol but high levels of hsCRP will benefit from statin therapy as a primary prevention strategy has recently being tested in the JUPITER trial. CDC and the American Heart Association, recommends to measure hsCRP in individuals determined to be at intermediate cardiovascular risk on the basis of traditional risk factors.[4]

hsCRP predicts early and late mortality rates in acute coronary ischemia, adding to the prognostic value of cardiac troponin, and predicts outcomes after coronary stent placement. At present, apparently healthy individuals with elevated levels of hsCRP should be advised to lose excess weight, increase physical activity , stop smoking, and consult with their physicians concerning the use of aspirin and lipid-lowering therapies. In the future, novel anti-inflammatory therapies that directly target the vascular endothelium may become available.

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