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REVIEW ARTICLE

# C-reactive protein, inflammation and coronary heart disease

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**KEYWORDS**

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**Abstract** Inflammation is widely considered to be an important contributing factor of the pathophysiology of coronary heart disease (CHD), and the inflammatory cascade is particularly important in the atherosclerotic process. In consideration of the important role that inflammatory processes play in CHD, recent work has been focused on whether biomarkers of inflammation may help to improve risk stratification and identify patient groups who might benefit from particular treatment strategies. Of these biomarkers, C-reactive protein (CRP) has emerged as one of the most important novel inflammatory markers. CRP an acute phase protein is synthesized by hepatocytes in response to proinflammatory cytokines, in particular interleukin-6. Many large-scale prospective studies demonstrate that CRP strongly and independently predicts adverse cardiovascular events, including myocardial infarction, ischemic stroke, and sudden cardiac death in individuals both with and without overt CHD. CRP is believed to be both a marker and a mediator of atherosclerosis and CHD. CRP plays a pivotal role in many aspects of atherogenesis including, activation of complement pathway, lipids uptake by macrophage, release of proinflammatory cytokines, induces the expression of tissue factor in monocytes, promotes the endothelial dysfunction and inhibits nitric oxide production. The commercial availability of CRP high sensitive assays has made screening for this marker simple, reliable, and reproducible and can be used as a clinical guide to diagnosis, management, and prognosis of CHD.



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## 1. Introduction

Cardiovascular diseases (CVDs) are the leading cause of mortality and morbidity all over the world, including India. CVD encompasses coronary heart disease (CHD), as well as congestive heart failure, stroke, peripheral artery disease, carotid artery disease, and aortoiliac disease.[1] CHD, also known as coronary artery disease, is the narrowing of the blood vessels, as a result of atherosclerosis that supply blood and oxygen to the heart. CHD can lead to unstable angina, myocardial infarction (MI), and heart failure.[2] According to World Health Organization (WHO) estimates, 17.3 million people died from CVDs in 2008, representing 30% of all global deaths. Of these deaths, an estimated 7.3 million were due to CHD and 6.2 million were due to stroke.[3] CHD is decreasing in many developed countries (due to improved prevention {in particular reduced cigarette smoking among adults, and lower average levels of blood pressure and blood cholesterol}, diagnosis, and treatment), but is increasing in developing and transitional countries, partly as a result of increasing longevity, urbanization, and lifestyle changes. In developed countries, CHD is predicted to raise 30–60% between 1990 and 2020. In developing countries, rates are predicted to increase by 120% in women and 137% in men from 1990 to 2020.[4]

During the past decades a great deal of knowledge concerning the pathophysiology of CHD has been achieved, and age (older than 40 years for men, 45 years for women), male sex, family history of CHD, smoking, hypertension, diabetes, obesity, high total cholesterol, low high density lipoprotein cholesterol (HDL-C), high low density lipoprotein cholesterol (LDL-C), high triglycerides, low physical activity, and accumulation of abdominal fat are some of the major risk factors.[5] However, despite identification of important risk factors, CHD remains the leading cause of death worldwide. Up to half of all events associated with CHD are reported to occur in apparently healthy individuals who have few or none of the traditional risk factors, including dyslipidemia. As a result, attention has increasingly turned to the role of other factors, such as inflammation, in the development of atherosclerosis and CHD.[6]

Atherosclerosis, the underlying pathology responsible for CHD, is an inflammatory disease. Recent observations suggest that the atherosclerotic process is characterized by a low-grade inflammation altering the endothelium of the coronary arteries and is associated with an increase level in markers of inflammation such as acute phase proteins and cytokines. Cumulative evidence indicates that inflammation, at both focal and systemic levels, plays a key role in destabilization and rupture of atherosclerotic plaques, leading to acute cardiovascular events.[7] In consideration of the important role that inflammatory processes play in determining plaque stability, recent work has focused on whether biomarkers of inflammation may help to improve risk stratification and identify patient groups who might benefit from particular treatment strategies. Among them, C-reactive protein (CRP), a prototype marker of the inflammatory process, is the most studied both as a causal factor and in the prediction of CHD.[8]

CRP is the forerunner in the hunt for inflammatory markers and is subject to intensive research in numerous studies worldwide. Unlike other markers of inflammation, CRP levels are stable over long periods, have no diurnal variation, can be measured inexpensively with available high-sensitivity assays, and have shown specificity in terms of predicting the risk of CHD.[9] CRP may have a role in the genesis of atherosclerotic lesion, since it reduces the expression of nitric oxide (NO) synthase and prostacyclin synthase, and binds LDL-C and promotes its uptake by macrophages, a key step in atherogenesis. CRP also up-regulates the expression of adhesion molecules on endothelial cell (EC). All these phenomena are associated with atherogenesis.[10] Multiple prospective cohort studies have established that increased CRP levels are associated with increased CHD risk in both genders, across a wide age range, and in primary as well as secondary prevention settings. These findings have been consistent in different populations with diverse ethnic backgrounds and in diverse clinical settings, and they have predicted risk of a variety of cardiovascular outcomes, including incident acute myocardial infarction (AMI), stroke, sudden cardiac death, peripheral artery disease and also incident diabetes and new onset hypertension. CRP levels have also been shown to predict risk of both recurrent

ischemia and death among those with stable and unstable angina, those undergoing percutaneous angioplasty, and those presenting to emergency rooms with acute coronary syndrome (ACS).[7,11]

## 2. Inflammation and atherosclerosis

Atherosclerosis is the most common pathological process that leads to CHD, a disease of large- and medium-sized arteries that is characterized by a formation of atherosclerotic plaques consisting of necrotic cores, calcified regions, accumulated modified lipids, inflamed smooth muscle cells (SMCs), ECs, leukocytes, and foam cells.[12] The word atherosclerosis comes from the Greek words "Athero" means gruel and corresponds to the necrotic core at the base of the atherosclerotic plaque, whereas "sclerosis" means hardening or induration, and corresponds to the fibrotic cap at the luminal edge of the plaque, and reflects quite well the macroscopic morphology of an atherosclerotic lesion, yellow-white thickening of the vessel wall with a hard fibrous cap in advanced lesion. Despite the first description of inflammation in coronary atherosclerosis 200 years back, it is only recently that there has been a wide acceptance of the role of inflammation in the pathogenesis of atherosclerosis and destabilization of the coronary artery plaque.[10] In 1999, Russel Ross was the first, who published that atherosclerosis is an inflammatory disease.[13] The "response to injury" theory on the pathophysiology of atherosclerosis is best acknowledged nowadays.

Atherosclerosis is characterized by a complex multifactorial pathophysiology. Inflammation in the vessel wall is now considered to play an essential role in the initiation, progression and the final steps of atherosclerosis, namely plaque destabilization and eventually plaque rupture. Histologically atheromatous plaques obtained at autopsy have demonstrated the presence of inflammatory mononuclear cells with foci of monocytes, macrophages and T lymphocytes in the arterial wall. Anatomically, the most common site of plaque rupture in ACS appears to occur in the shoulder region, where inflammatory cells are most prominent and might serve to compromise the integrity of the surrounding connective tissue. From a pathological point of view, all stages of the atherosclerotic process, from its initiation to plaque rupture, might be considered an inflammatory response to injury and endothelial dysfunction. Damage to the endothelial wall triggers a cascade of events that modulates the inflammatory response, leading to the recruitment of white blood cells into the blood vessel wall, where they give rise to abnormal foam cells and initiate the development of atherosclerotic lesions.[14]

## 3. Pathophysiology of atherosclerosis

The endothelium is an active monolayer of cells lining the lumen of the vessels, separating the vascular wall from the circulating blood. Under normal conditions, the ECs of the arterial wall resist adhesion and aggregation of leukocytes and promote fibrinolysis. When activated by stimuli such as hypertension, smoking, an unhealthy diet, obesity, insulin resistance, inflammation or other types of injuries, the ECs express a series of adhesion molecules that selectively recruit various classes of leukocytes. Blood monocytes, the most numerous of the inflammatory cells that populate plaques, adhere to the dysfunctional endothelial surface by binding to leukocyte adhesion molecules not expressed by normal ECs, but induced by mediators associated with risk factors such as proinflammatory cytokines, angiotensin (AT) II, and oxidized lipoproteins. Once the monocytes adhere to the activated endothelium, proinflammatory proteins known as chemokines provide a chemotactic stimulus that induces them to enter the intima. Within the intima, the monocytes mature into macrophages, which express scavenger receptors that allow them to engulf modified lipoprotein particles. The cytoplasm becomes engorged with lipid particles, giving the macrophages the typical microscopic frothy appearance of the foam cells found in atherosclerotic lesions.[15–17]

At the same time, other inflammatory mediators, including activated T cells and mast cells, also attach themselves to the endothelium. Activation of macrophages, T lymphocytes, and SMCs leads to the release of additional mediators, including adhesion molecules, cytokines, chemokines, and growth factors, all of which play important roles in atherogenesis. All of these inflammatory cells eventually contribute to the formation of the atheromatous lesion, which consists of a lipid pool protected by a fibrous cap.[18] Over time the plaque attract deposits of calcium; calcification of the artery is an important marker for the development of atherosclerosis. Finally, endothelium-derived NO, a vasoactive molecule that helps to maintain vascular tone, is reduced at the site of vascular injury. Decreased NO production is implicated in the clinical course of all known CVD. NO has a number of intracellular effects that lead to vasorelaxation, endothelial regeneration, inhibition of leukocyte chemotaxis, and platelet adhesion and aggregation. Endothelium damage induced by atherosclerosis leads to the reduction in bioactivity of endothelial NO synthase with subsequent impaired release of NO together with a local enhanced degradation of NO by increased generation of reactive oxygen species with subsequent cascade of oxidation-sensitive mechanisms in the arterial wall. Therefore, a reduction in NO activity contributes to a pro-inflammatory and prothrombotic milieu.[19]

Although the possible events that can initiate fatty streak formation remain controversial, over the last few decades, a plausible model linking lipids and inflammation to atherogenesis has emerged. LDL, which may be modified by oxidation, glycation (in diabetes), aggregation, association with proteoglycans, or incorporation into immune complexes, is a major cause of injury to the endothelium and underlying smooth muscle. When LDL particles become trapped in an artery, they can undergo progressive oxidation and be internalized by macrophages by means of the scavenger receptors on the surfaces of these cells. The internalization leads to the formation of lipid peroxides and facilitates the accumulation of cholesterol esters, resulting in the formation of foam cells.[13]

In most patients MIs occur as a result of erosion or uneven thinning and rupture of the fibrous cap, often at the shoulders of the lesion where macrophages enter, accumulate, and are activated and where apoptosis may occur. Degradation of the fibrous cap may result from elaboration of metalloproteinases such as collagenases, elastases, and stromelysins. Activated T cells may stimulate metalloproteinase production by macrophages in the lesions, which promotes plaque instability and further implicates an immune response. These changes may also be accompanied by the production of tissue factor procoagulant and other hemostatic factors, further increasing

the possibility of thrombosis.[13] The results may be either coronary or cerebral infarction, depending on the duration of the thrombosis and the location of the associated vasoconstriction.

## 4. C-reactive protein (CRP)

### *4.1. Historical perspectives*

CRP was first discovered in 1930 by William Tillet and Thomas Francis at the Rockefeller Institute for Medical Research, in New York. In studying the blood of patients suffering from acute Streptococcus pneumonia infection, it was found that the sera of these patients formed a precipitin with an extract from the streptococcal bacterium. The extract was originally labeled Fraction C, and was later confirmed as a polysaccharide. Hence, as a result of its reactivity with the C polysaccharide of the Streptococcus cell wall, the 'substance' in the sera was named CRP.[20] A decade later, Oswald Avery and Maclyn McCarty-the research team who originally described the "transforming principle" and the concept that genes are made of DNA also described CRP as an "acute-phase reactant" that was increased in serum of patients suffering from a spectrum of inflammatory stimuli, including myocarditis and the inflammation associated with rheumatic fever.[21–23]

Early clues that this inflammatory biomarker might be linked to atherothrombosis are evident in 2 case reports presented by Gunnar Lofstrom from the State Bacteriologic Laboratory in Stockholm in 1943, in which increases in CRP following AMI was described.[24] In the mid 1950s, case series presented by Irving Kroop and others indicated that CRP concentrations consistently increased after coronary ischemia and myocardial necrosis.[25] Despite these early findings, it was not until the 1990s that cardiovascular interest in CRP was revitalized. In mid 1990s, immunoassays for CRP (hs-CRP), with greater sensitivity than those previously routine uses, revealed that increased CRP values, even within the range previously considered normal, strongly predict future coronary events.

### *4.2. Structure of CRP*

CRP belongs to the pentraxin family of calcium dependent ligand-binding plasma proteins. The human CRP molecule is composed of five identical non-glycosylated polypeptide subunits each containing 206 amino acid residues. The protomers are non-covalently associated in an annular configuration with cyclic pentameric symmetry (Fig. 1). The pentraxin family, named for its electron micrographic appearance from the Greek penta (five) ragos (berries), is highly conserved in evolution.[26,27]

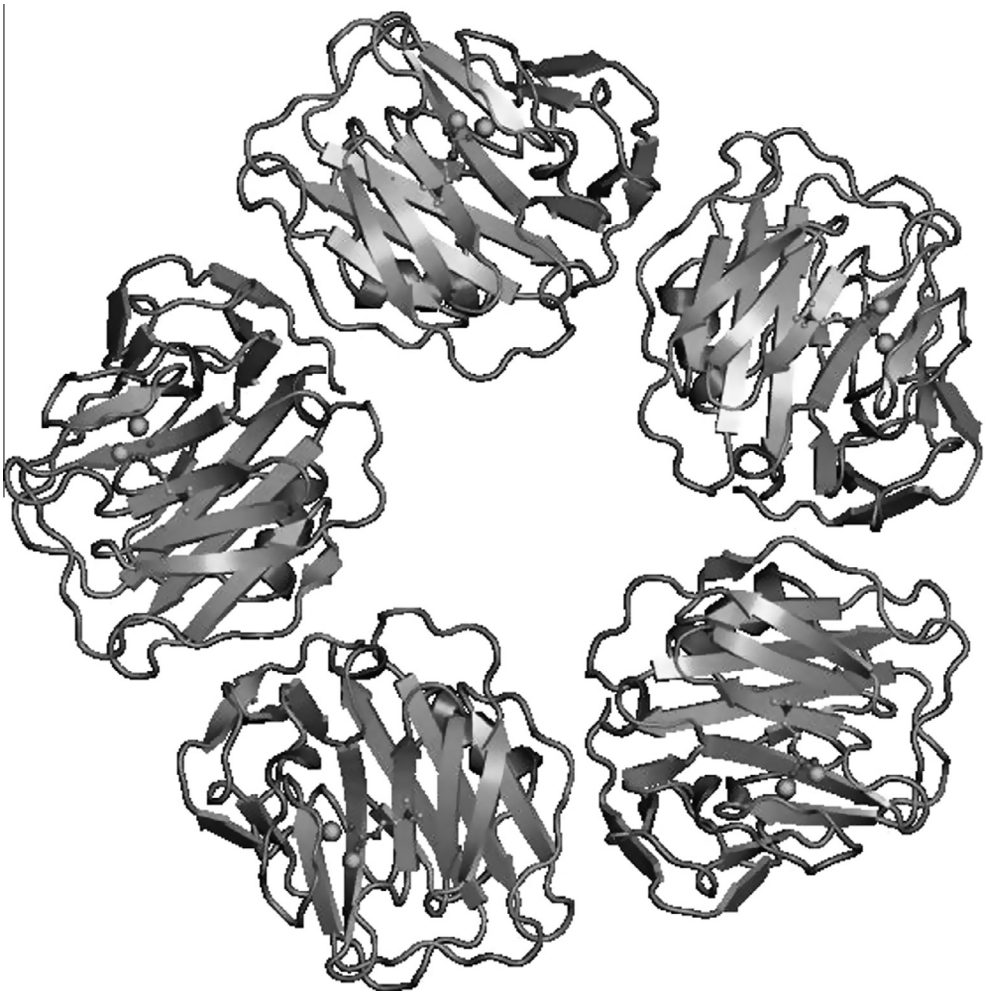

**Figure 1** Pentameric structure of CRP.[27]

Each CRP protomer has the flattened beta-jellyroll lectin fold and bears on one face, the B or binding face, a pocket which contains two calcium ions bound just 4 Å apart by coordination with protein carboxylate and amide side chains derived from loops that congregate on one face of the protomer core. These calcium atoms are essential for all physiological ligand binding by CRP and also markedly stabilize both the structure of the protomer and the integrity of the native pentamer.[28] Upon dissociation of its pentameric structure, CRP subunits undergo a spontaneous and irreversible conformational change. The loss of the pentameric structure of CRP results in modified or monomeric CRP (mCRP), which is a naturally occurring form of CRP and it is a tissue-based rather than a serum based molecule. mCRP is less soluble than CRP and tends to aggregate, and it has been described to induce mRNA of chemokines and the expression of adhesion molecules in human cultured coronary artery ECs.[29] In human, the CRP gene is located on chromosome 1q23, in a conserved genetic region, which codes for proteins important for immune system as well as cell to cell communication.[30] The major part of the CRP present in the plasma comes from the liver, where the synthesis of CRP is mainly regulated by interleukin-6 (IL-6), which in turn is up-regulated by other inflammatory cytokines such as IL-1 and tumor necrosis factor (TNF)-α. CRP also produced locally in atherosclerotic lesions by SMCs lymphocytes and monocytic cells.[29]

### *4.3. Biological functions of CRP*

Most functions of CRP are easily understood in the context of the body's defenses against infective agents. CRP provides the first line of defense of pathogen. Despite structural differences with immunoglobulin molecule, CRP shares similar functional properties with the immunoglobulins, such as, the ability to promote agglutination, activation of the classical complement pathway, bacterial capsular swelling, phagocytosis and precipitation of polycationic and polyanionic compounds.[31] By analogy with antibodies, it is therefore possible that CRP might contribute both to host defence against infection and enhancement of inflammatory tissue damage. Other distinctive characteristics of CRP are its binding specificities and its site of synthesis which confer it to a new super family of proteins. Phosphocholine is the natural ligand to which CRP binds with highest affinity and this key ligand is ubiquitous as the polar head group of phosphatidlyl choline in cell membranes and plasma lipoproteins. CRP does not bind to all materials containing phosphocholine as the residues must be 'available' or in an appropriate sterochemical configuration. Thus CRP binds to dead or damaged cells in which significant amounts of lysophosphatidyl choline are present, but not the surface of living healthy cells.[28] CRP also binds to a variety of other autologous and extrinsic ligands, and it aggregates or precipitates the cellular, particulate, or molecular structures bearing these ligands. Autologous ligands include native and modified plasma lipoproteins, damaged cell membranes, a number of different phospholipids and related compounds, small nuclear ribonucleoprotein particles, and apoptotic cells. Extrinsic ligands include many glycan, phospholipid, and other constituents of microorganisms, such as capsular and somatic components of bacteria, fungi, and parasites, as well as plant products.[26]

### *4.4. Circulating CRP levels*

Surprisingly in view of the sensitivity, speed, and range of the CRP response, subjects in the general population tend to have stable CRP concentrations characteristic for each individual, apart from occasional spikes presumably related to minor or subclinical infections, inflammation, or trauma. In healthy young adult volunteer blood donors, the median concentration of CRP is 0.8 mg/L, the 90th centile is 3.0 mg/L, and the 99th centile is 10 mg/L, but, following an acute-phase stimulus, values may increase from less than 50 μg/L to more than 500 mg/L, that is, 10,000-fold.[26] Importantly, acute-phase CRP values show no relationship to fasting state or diurnal patterns and have a long half-life. Liver failure impairs CRP production, but no other intercurrent pathologies and very few drugs reduce CRP values unless they also affect the underlying pathology providing the acute-phase stimulus. After a stimulus, within 6 h, plasma CRP levels increase above 5 mg/L and reach the maximum within 48 h. CRP can rise up to 10,000-fold in acute inflammation, such as during infection. After that, the level of CRP returns to very low reference values in plasma with the same speed. The half-life of CRP in plasma is approximately 19 h and is constant during various conditions in healthy and sick people. Therefore the only factor determining the level of CRP is its production speed, which directly reflects the intensity of pathological process.[30]

### *4.5. Clinical utility of CRP*

The attention focused on CRP reflects in part the fact that it has assay characteristics conducive for clinical use, commercially robust assay is available widespread, it is very stable in serum or plasma with very marginal fluctuations, more cost-effective than the emerging risk markers and has been proven to orchestrate atherosclerosis.[32] It is easily measured, and standardized high-sensitivity immunoassays (detecting CRP concentrations $< 5$ mg/L) provide similar results in fresh, stored, or frozen plasma, reflecting the stability of the protein, which has led CRP to emerge as a robust clinical marker. Moreover, there is no diurnal variation and no significant difference in the distribution curve between men and women. Serum levels are independent from age and ethnicity. All these factors make it a relatively stable serum protein compared with many other markers. In addition to in vitro and in vivo studies, a large number of studies on the utility of CRP as a clinical marker for CHD have been performed.[8] Although CRP is a nonspecific inflammatory marker, it is a strong independent predictor for CHD risk and events. Epidemiological studies and clinical trials have found that CRP is a strong independent predictor of future CHD risk. Circulating CRP values correlate closely with other markers of inflammation, some of which show similar, albeit generally less significant, predictive associations with coronary events. Furthermore, the intrinsic biological properties of CRP as an acute-phase reactant are especially favorable for its use as a sensitive quantitative systemic readout of the acute-phase response. In contrast, none of the other systemic markers of inflammation, whether upstream cytokine mediators, other sensitive acute-phase proteins such as serum amyloid A, negative acute-phase proteins such as albumin, or cruder multifactorial measures such as erythrocyte sedimentation rate or polymorph count, has such robust and desirable

characteristics. The inherent properties of CRP and its behavior may sufficiently explain why it provides closer associations and better predictions than other markers of inflammation.[26]

In addition to assessing future CHD risk in asymptotic individuals, growing bodies of studies suggest that elevation of hs-CRP levels predicts a poor cardiovascular prognosis. CRP levels predict clinical outcomes in acute coronary syndromes and may be used in conjunction with troponin I or T levels to identify high-risk patients for more aggressive management with antiplatelet agents and statins. Similarly, in patients undergoing percutaneous coronary interventions, CRP levels may alert the interventional cardiologist for closer monitoring of the patients or more aggressive management. Components of the metabolic syndrome (i.e., central obesity, increased plasma triglyceride concentrations, low plasma concentrations of HDL-C, hypertension, and increased concentrations of blood glucose) correlate with increased plasma CRP concentrations, and CRP measurement contributes to risk prediction in individuals with the metabolic syndrome.[33] Furthermore, CRP levels could be used to motivate patients to modify their lifestyles more aggressively. Recent studies have shown that losing weight, diet, exercise, cessation of smoking and controlling diabetes also lower CRP levels. Thus, patients can use their CRP levels as an inflammation fitness score to monitor improvement in their cardiovascular health. Some medicines can also reduce CRP levels such as aspirin, statins, thiazolidinediones, AT-converting enzyme inhibitors and thienopyridines.[34]

Concerning hs-CRP level and CHD risk, a level of less than 1 mg/L indicates lower risk, a level between 1 and 3 mg/L indicates moderate risk and a level higher than 3 mg/L indicates a higher risk – that is simple enough. But the continuum extends beyond that. The patients with the very highest levels of hs-CRP; 5–10, 10–20, or even greater than 20 mg/L are, in fact, at the very highest risk. These are not false positives. These data help to explain why those with periodontal disease, arthritis, and other systemic inflammatory disorders all have higher vascular risk. Perhaps inflammation from any cause has an adverse effect on the vascular endothelium.[35] In current strategies of global risk assessment, lipid testing is the only blood test routinely recommended. However, CRP evaluation may provide a simple and inexpensive method to improve global risk prediction and compliance with preventive approaches, when used as in addition to traditional lipid profiles.[9]

To improve cardiovascular risk stratification in primary prevention populations, an expert panel assembled by the Centers for Disease Control and Prevention and the American Heart Association termed CRP an independent marker of cardiovascular risk. The panel recommends the use of CRP as part of global risk prediction in asymptomatic individuals, particularly those deemed at intermediate risk for CVD by traditional risk factors.[36] The CRP concentration is thus a very useful nonspecific biochemical marker of inflammation, measurement of which contributes importantly to (a) screening for organic disease, (b) monitoring of the response to treatment of inflammation and infection {Serial measurements reflects activity and response to treatment and can be used for monitoring}, and (c) detection of intercurrent infection in immuno-compromised individuals, and in the few specific diseases characterized by modest or absent acute-phase responses.

### *4.6. High sensitive CRP (hs-CRP)*

The recent emphasis in cardiovascular medicine on "high-sensitivity" or "highly sensitive" CRP, abbreviated as so-called hs-CRP, seems to have created a false impression in some quarters that this is somehow a different analyte from "conventional" CRP. This is incorrect.[26] It is very important to recognize that the analyte designated as hs-CRP is just CRP itself, not anything new or different and in particular is not a novel analyte with any special relationship to CHD. hs-CRP is the same exquisitely sensitive and entirely nonspecific systemic marker of infection, inflammation, tissue damage and/or almost any form of adverse non-physiological stress as the CRP, which has been extensively studied and used clinically for over 75 years.[28] Formerly, assays for CRP, using a polyclonal antibody had a sensitivity of about 5 mg/L. With these assays, the level of CRP was detectable only during significant inflammation in most individuals. In the mid of 1990s, a new method enzyme-linked immunosorbent assay (ELISA) was established to evaluate the level of hs-CRP, which has much higher sensitivity (to quantify CRP throughout its normal range) then classic methods used previously.[30] These lower levels toward the upper end of normal reflect low-grade inflammation and have a predictive value of future risk for CHD events.[37]

### *4.7. Atherosclerosis, inflammation, and CRP*

The possibility that CRP might have proatherogenic actions was first suggested in 1982 by the discovery of its specific binding to LDL and VLDL and was supported by its detection in atherosclerotic plaque.[28] Inflammatory mechanisms play a central role in all phases of atherosclerosis, from the initial recruitment of circulating leukocytes to the arterial wall to the rupture of unstable plaques, which results in the clinical manifestations of the disease. CRP may be involved in each of these stages by direct influencing processes such as complement activation, apoptosis, vascular cell activation, monocyte recruitment, lipid accumulation and thrombosis. CRP is one of the substances present in the atherosclerotic lesion, more specifically in the vascular intima, where it co-localizes with monocytes, monocyte-derived macrophages and lipoproteins. This localization makes a direct contribution to the atherosclerotic process.[29] The direct pro-atherogenic effects of CRP extend beyond the endothelium to the vascular smooth muscle. CRP plays a pivotal role in many aspects of atherogenesis as described briefly below (Fig. 2):

- Activation of the classical pathway of the complement system, through this action, CRP directly amplifies and facilitates innate immunity, a process that has already been associated with initiation and progression of CHD.[29]
- CRP increases LDL uptake into macrophages and enhances the ability of macrophages to form foam cells. It also binds the phosphocholine of oxidized LDL.
- CRP inhibits endothelial NO synthase expression in ECs. NO has important anti-atherogenic effects, including decreased platelet aggregation, vasoconstriction, and smooth muscle cell proliferation.

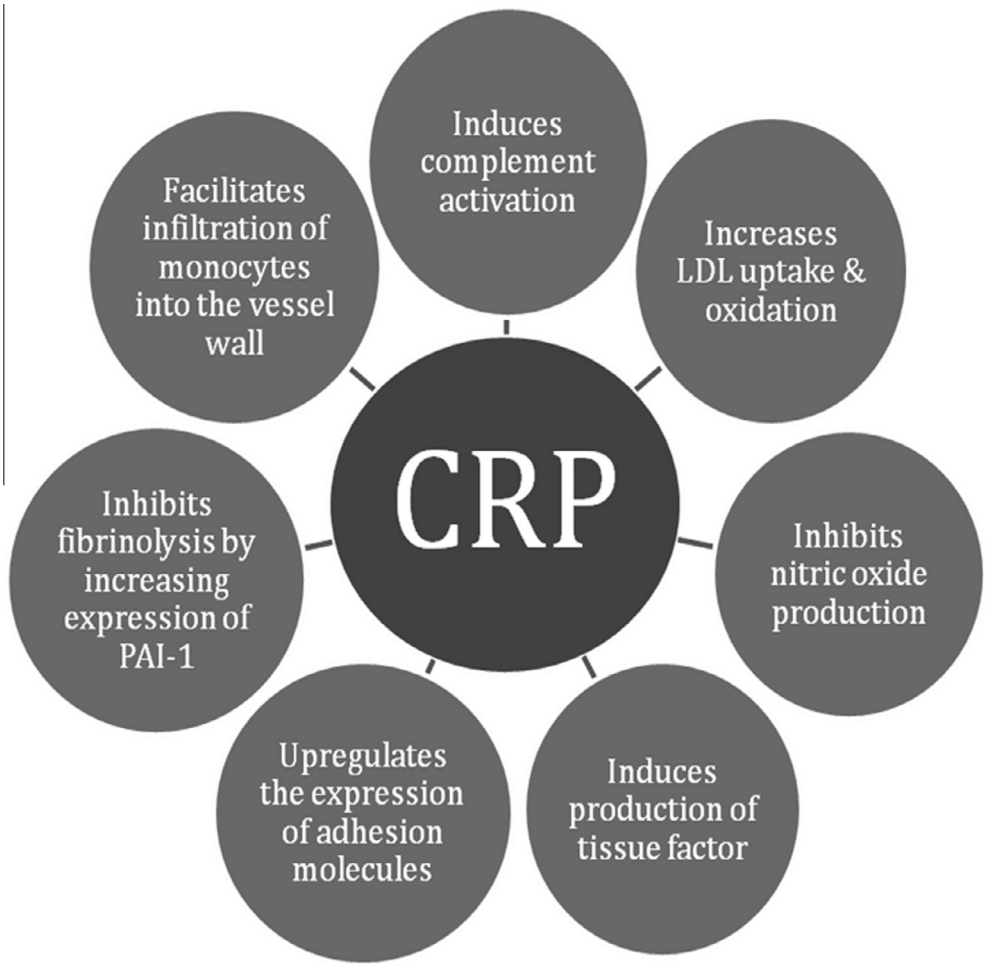


**Figure 2** Representation of CRP-mediated effects on atherosclerosis and CHD. LDL; low density lipoprotein, PAI; plasminogen activator inhibitor.

- CRP activates macrophages to secrete tissue factor, a powerful procoagulant, which can lead to disseminated intravascular coagulation and ultimately to thrombosis during inflammatory states.
- CRP upregulates the expression of adhesion molecules in ECs that can attract monocytes to the site of injury.[14]
- CRP increases PAI-1 expression and activity. PAI-1 is a protease inhibitor that regulates fibrinolysis by inhibiting tissue plasminogen activator. Increased PAI-1 indicates lowered fibrinolysis and thus leads to atherogenesis.[32]
- CRP also indirectly affects specific immune response, during atherogenesis, through the increase of IL-12 production from macrophages, with the subsequent induction of CD4 + T lymphocytes differentiation and Interferon gamma production.[8]

## 5. CRP and coronary heart disease

Elevated CRP has been associated with many non-communicable diseases such as CHD, ischemic stroke, insulin resistance, hypertension, metabolic syndrome and peripheral artery disease. The most extensively studied area is its role as a marker and a maker of CHD. Several landmark large prospective clinical case-control studies on middle-aged men (Physician's Health Study,[38] Monitoring Trends and Determinants in Cardiovascular Disease[39]), postmenopausal women (Women Health Study[40]), and elderly men and women (Cardiovascular Health Study Rural Health Promotion Project[41]) have identified CRP as a strong, independent risk factor for CHD. In some recent studies Arroyo Espliguero et al. [42] and Raposeiras Roubín[43] concluded that CRP is an independent predictor of adverse cardiac events.

An association between sustained high values of CRP following AMI and adverse outcomes was first reported in 1982[44] and subsequent large studies have shown that increased peak and post-infarct CRP concentrations are significantly associated with increased incidence of cardiac complications including heart failure and cardiac death, apparently independently of other predictors[28]. Tissue necrosis is a potent acute-phase stimulus, and following MI, there is a major CRP response, the magnitude of which reflects the extent of myocardial necrosis. Myocardial necrosis due to abrupt closure of coronary artery, in case of AMI, leads to a systemic and regional humoral and cellular inflammatory response aiming to promote the local myocardial healing process and scar formation. In the early phase of MI, cytokines play an important cytoprotective role, mainly by reducing cell apoptosis. Pro-inflammatory cytokines are the starting promoters of the humoral post-MI healing process. They directly interfere with the myo-

cardial contractility, the vascular endothelial function, and the recruitment of other inflammatory cells. Plasma CRP concentration increases following the cytokines activation in the initial hours of MI. CRP binds to phosphocholine groups of necrotic myocardial cell membranes, facilitating complement activation, and thus promoting further inflammatory response, injury of myocardial cells, and expansion of necrosis.[45]

In patients with ACS, an increase in the CRP level at admission is associated with a poorer short-term and long-term prognosis. The majority of authors concur in that the admission CRP value reflects the baseline inflammatory status of the patient; thus, patients with ACS and high CRP levels at admission usually experience more cardiovascular complications during follow-up. Patients with ACS and higher CRP may represent a group with hyper-responsiveness of the inflammatory system, which might exaggerate the acute-phase reaction and increase immune system activation, which may in turn mediate myocardial damage and promote cardiac complications. This may be more pronounced in patients with non-STEMI than in those with STEMI, due to a higher atherosclerotic burden. As reported by several studies, elevated CRP levels after MI are associated with adverse clinical outcome, including cardiac rupture, heart failure, and cardiac death. The higher the maximum CRP recorded, the more severe the infarction suffered, the greater the likelihood of ventricular remodeling, the lower the ejection fraction, and the greater the risk of heart failure, heart rupture, and death.[46]

The likely mechanism of CRP pathogenicity is therefore binding of abundant CRP to the ligands exposed in dead and damaged cells, triggering substantial complement activation with release of chemotactic factors and opsonization of cells in and around the lesion, leading to enhanced infiltration by inflammatory cells and consequent bystander damage. The terminal complement sequence may also directly kill cells which would otherwise survive and the end result is death of more myocardial tissue than would be killed by ischemia alone.[28]

## 6. Conclusion

CHD is the leading cause of death and disability in developed nations and is increasing rapidly in the developing world. Up to half of all events associated with CHD are reported to occur in apparently healthy individuals who have few or none of the traditional risk factors, including dyslipidemia. As a result, attention has increasingly turned to the role of other factors, such as inflammation, in the development of atherosclerosis and CHD. Recent observations suggest that the atherosclerotic process is characterized by a low-grade inflammation altering the endothelium of the coronary arteries and is associated with an increase level in markers of inflammation. In an attempt to improve global cardiovascular risk prediction, considerable interest has focused on CRP. CRP is not only an excellent biomarker of inflammation, but it is also a direct participant in atherogenesis. Many studies have demonstrated that increased CRP concentrations are associated with an increased risk of MI, stroke, peripheral arterial disease, and sudden cardiac death. Unlike other markers of inflammation, CRP levels are stable over long periods, have no diurnal variation, can be measured inexpensively with available high-sensitivity assays, and have shown specificity in terms of predicting the risk of cardiovascular disease. When combined with lipid screening, CRP improves global risk prediction in patients who would otherwise not be identified for primary prevention by lipid assessment alone.

## 7. Disclosure statement

None of the authors have a competing interest to disclose.

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## References

1. Gupta R, Joshi P, Mohan V, Reddy KS, Yusuf S. Epidemiology and causation of coronary heart disease and stroke in India. *Heart* 2008;**94**:16–26.
2. Imes CC, Austin AM. Low-density lipoprotein cholesterol, apolipoprotein B, and risk of coronary heart disease: from familial hyperlipidemia to genomics. *Biol Res Nurs* 2012;**15**:292–308.
3. World Health Organization (WHO). *Global atlas on cardiovascular disease prevention and control*. Geneva, Switzerland; 2011.
4. Murray CJL, Lopez AD. Alternative projections of mortality and disability by cause 1990–2020: global burden of disease study. *Lancet* 1997;**349**:1498–504.
5. Torpy JM, Burke AE, Glass RM. Coronary heart disease risk factors. *JAMA* 2009;**302**:2388.
6. Clearfield MB. C-reactive protein: a new risk assessment tool for cardiovascular disease. *J Am Osteopath Assoc* 2005;**105**:409–16.
7. Madjid M, Willerson JT. Inflammatory markers in coronary heart disease. *Br Med Bull* 2011;**100**:23–38.
8. Calabro P, Golia E, Yeh ET. Role of C-reactive protein in acute myocardial infarction and stroke: possible therapeutic approaches. *Curr Pharm Biotechnol* 2012;**13**:4–16.
9. Devaki RN, Basavana Gowdappa H, Suma MN, Prashanth V, Akila P, Anjali Devi BD. A study of C-reactive protein and its relationship with CHD and lipid metabolism. *Int J Pharm Sci Rev Res* 2011;**6**:125–7.
10. Mehta JL, Sukhija R, Romeo F, Sepulveda JL. Value of CRP in coronary risk determination. *Indian Heart J* 2007;**59**:173–7.
11. Greenland P, Alpert JS, Beller GA, Benjamin EJ, Budoff MJ, Fayad ZA, et al. 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults: a report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines. *Circulation* 2010;**122**:e584–636.
12. Galkina E, Ley K. Immune and inflammatory mechanisms of atherosclerosis. *Annu Rev Immunol* 2009;**27**:165–97.
13. Ross R. Atherosclerosis – an inflammatory disease. *N Engl J Med* 1999;**340**:115–26.
14. Pfützner A, Schöndorf T, Hanefeld M, Forst T. High-sensitivity C-reactive protein predicts cardiovascular risk in diabetic and nondiabetic patients: effects of insulin-sensitizing treatment with pioglitazone. *J Diabetes Sci Technol* 2010;**4**:706–16.
15. Mestas J, Ley K. Monocyte-endothelial cell interactions in the development of atherosclerosis. *Trends Cardiovasc Med* 2008;**18**:228–32.
16. Rader DJ, Daugherty A. Translating molecular discoveries into new therapies for atherosclerosis. *Nature* 2008;**451**:904–13.
17. Libby P, Okamoto Y, Rocha VZ, Folco E. Inflammation in atherosclerosis: transition from theory to practice. *Circ J* 2010;**74**:213–20.

18. Willerson JT, Ridker PM. Inflammation as a cardiovascular risk factor. *Circulation* 2004;**109**:II2–II10.
19. Napoli C, de Nigris F, Williams-Ignarro S, Pignalosa O, Sica V, Ignarro LJ. Nitric oxide and atherosclerosis: an update. *Nitric oxide* 2006;**15**:265–79.
20. Tillet WS, Francis T. Serological reactions in pneumonia with a non-protein somatic fraction of the Pneumococcus. *J Exp Med* 1930;**52**:561–71.
21. Abernathy T, Avery O. The occurrence during acute infections of a protein not normally present in the blood. I. Distribution of the reactive protein in patients serum and the effect of calcium on the flocculation reaction with C polysaccharide of pneumococcus. *J Exp Med* 1941;**73**:173–82.
22. Macleod C, Avery O. The occurrence during acute infections of a protein not normally present in the blood. II. Isolation and properties of the reactive protein. *J Exp Med* 1941;**73**:183–90.
23. McCarty M. The occurrence during acute infections of a protein not normally present in the blood. IV. Crystallization of the C-reactive protein. *J Exp Med* 1947;**85**:491–8.
24. Lofstrom G. Nonspecific capsular swelling in pneumococci: a seriologic and clinical study. *Acta Med Scand Suppl* 1943;**141**:3–98.
25. Kroop IG, Shackman NH. Level of C-reactive protein as a measure of acute myocardial infarction. *Proc Soc Exp Biol Med* 1954;**86**:95–7.
26. Pepys MB, Hirschfield GM. C-reactive protein: a critical update. *J Clin Invest* 2003;**111**:1805–12.
27. <http://en.wikipedia.org/wiki/C-reactive_protein>.
28. Casas JP, Shah T, Hingorani AD, Danesh J, Pepys MB. C-reactive protein and coronary heart disease: a critical review. *J Int Med* 2008;**264**:295–314.
29. Paffen E, DeMaat MP. C-reactive protein in atherosclerosis: a causal factor? *Cardiovasc Res* 2006;**71**:30–9.
30. Bucova M, Bernadic M, Buckingham T. C-reactive protein, cytokines and inflammation in cardiovascular diseases. *Bratisl Lek Listy* 2008;**109**:333–40.
31. Ansar W, Ghosh S. C-reactive protein and the biology of disease. *Immunol Res* 2013;**56**:131–42.
32. Davis FJ, Vidyasagar S, Maiya GA. C-reactive protein and coronary heart disease - risk marker or risk factor? *J Clin Sci Res* 2012;**1**:178–86.
33. Packard RR, Libby P. Inflammation in atherosclerosis: from vascular biology to biomarker discovery and risk prediction. *Clin Chem* 2008;**54**:24–38.
34. John JM, Bhatt DL. Emerging risk factors for atherosclerosis. *Indian Heart J* 2007;**59**:28–37.
35. Ridker PM, Cannon CP, Morrow D, Rifai N, Rose LM, McCabe CH, et al. C-reactive protein levels and outcomes after statin therapy. *N Engl J Med* 2005;**352**:20–8.
36. Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon 3rd RO, Criqui M, et al. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: a statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. *Circulation* 2003;**107**:499–511.
37. Camhi SM, Stefanick ML, Ridker PM, Young DR. Changes in C-reactive protein from low-fat diet and/or physical activity in men and women with and without metabolic syndrome. *Metabolism* 2009;**59**:54–61.
38. Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. *N Engl J Med* 1997;**336**:973–9.
39. Koenig W, Sund M, Fröhlich M, Fischer HG, Löwel H, Döring A, et al. C-Reactive protein, a sensitive marker of inflammation, predicts future risk of coronary heart disease in initially healthy middle-aged men: results from the MONICA (Monitoring Trends and Determinants in Cardiovascular Disease) Augsburg Cohort Study, 1984 to 1992. *Circulation* 1999;**99**:237–42.
40. Ridker PM, Buring JE, Shih J, Matias M, Hennekens CH. Prospective study of C-reactive protein and the risk of future cardiovascular events among apparently healthy women. *Circulation* 1998;**98**:731–3.
41. Tracy RP, Lemaitre RN, Psaty BM, Ives DG, Evans RW, Cushman M, et al. Relationship of C-reactive protein to risk of cardiovascular disease in the elderly. Results from the Cardiovascular Health Study and the Rural Health Promotion Project. *Arterioscler Thromb Vasc Biol* 1997;**17**:1121–7.
42. Arroyo Espliguero R, Avanzas P, Quiles J, Kaski JC. Predictive value of coronary artery stenoses and C-reactive protein levels in patients with stable coronary artery disease. *Atherosclerosis* 2009;**204**:239–43.
43. Raposeiras Roubín S, Barreiro Pardal C, Roubín-Camiña F, Ocaranza Sanchez R, Alvarez Castro E, Paradela Dobarro B, et al. High-sensitivity C-reactive protein predicts adverse outcomes after non-ST-segment elevation acute coronary syndrome regardless of GRACE risk score, but not after ST-segment elevation myocardial infarction. *Rev Port Cardiol* 2013;**32**:117–22.
44. de Beer FC, Hind CRK, Fox KM, Allan R, Maseri A, Pepys MB. Measurement of serum C-reactive protein concentration in myocardial ischaemia and infarction. *Br Heart J* 1982;**47**:239–43.
45. Swiatkiewicz I, Kozinski M, Magielski P, Fabiszak T, Sukiennik EP, Navarese EP, et al. Value of CRP in predicting left ventricular remodeling in patients with a first ST-segment elevation myocardial infarction. *Mediators Inflamm* 2012;**2012**:250867.
46. Habib SS, Kurdi MI, Aseri ZA, Suriya MO. CRP levels are higher in patients with ST elevation than non-ST elevation acute coronary syndrome. *Arq Bras Cardiol* 2011;**961**:13–7.