

REVIEWS

C - reactive protein: An inflammatory marker with specific role in physiology, pathology, and diagnosis

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Abstract

C-reactive protein (CRP), an acute phase protein belonging to pentraxin family of proteins, increases 1000-fold or more in concentration in blood during the occurrence of an injury, inflammation or tissue death. CRP is known to be involved in conjugation of pathogens to induce their destruction by complement system and is also studied as a marker of inflammation, disease activity and a diagnostic adjunct. This review focuses on the diagnostic significance of CRP in various disease conditions as well as the established and controversial evidence on its physiological role.

Introduction

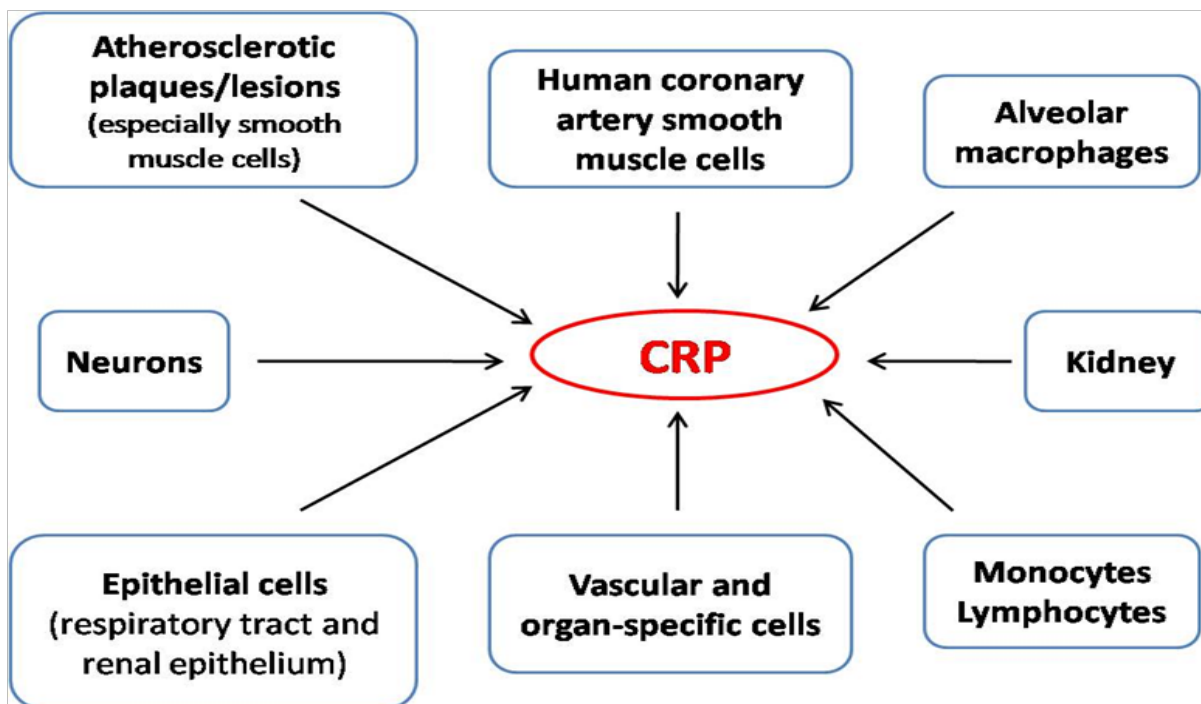
C-reactive protein (CRP) is one of the common test parameters used in clinical practice, to assess, diagnose, and prognose inflammation. However, the role played by CRP in physiological processes is not clearly elucidated. CRP, belonging to pentraxin family of proteins shows a 1000-fold or more increase in concentration during the occurrence of an injury, inflammation or tissue death.¹ The plasma half-life of CRP is about 19 hours and is constant under all conditions of health and disease.^{2, 3} In addition to CRP, the levels of few other proteins termed as acute phase proteins (APR) are also increased during inflammation. CRP, the first acute-phase protein to be described, is a sensitive systemic marker of inflammation and tissue damage.^{2, 4} Precise response and ease of assay have made CRP an ideal marker of inflammation. CRP was discovered in 1930 by William Tillett and Thomas Francis of Rockefeller University.⁵ The researchers have reported that a third serologic fraction or 'fraction C' isolated from pneumococcus infected patients, was different from capsular polysaccharide and nucleoprotein fractions detectable by specific antibody response.⁵ Oswald Avery and Maclyn McCarty, who postulated the 'transforming principle' and the concept that genes are made of DNA, also described that CRP as an 'acute-phase reactant' that was found to be increased in serum of patients having a spectrum of inflammatory stimuli.^{6, 7} Volanakis and Kaplan later identified the specific ligands that bind to CRP.⁸ CRP was found to have the function of conjugating pathogens

and inducing their destruction by complement system. It was also studied as a screening marker of inflammation, disease activity, and as a diagnostic adjunct.⁹ The exact role of CRP as an acute phase protein needs to be evaluated further. This review focuses on the diagnostic significance of CRP in various disease conditions as well as the established and controversial evidence on its physiological role.

Production of CRP

CRP is produced in many sites within the human body (Figure 1). It is produced in the liver in response to IL-6. Products of activated monocytes in Hep 3B cells induce the production of human serum amyloid A (SAA) protein and CRP, but not by IL-1 β , TNF- α , or some hepatocyte-stimulating factor preparations. It is also produced in very limited concentration by non-hepatic cells like neurons, atherosclerotic plaques, monocytes, Kupffer cells and lymphocytes.^{1, 10, 11} Studies have shown that epithelial cells of both respiratory tract and renal epithelium can also produce CRP under certain circumstances.^{12, 13} Recent studies have demonstrated that human coronary artery smooth muscle cells could also synthesize CRP upon stimulation by inflammatory cytokines.^{14, 15} Cogent data have indicated that the protein is also produced by the atherosclerotic lesions (especially by smooth muscle cells and macrophages), kidneys, neurons, and alveolar macrophages.¹⁶ Additionally, there is evidence to suggest that lipid peroxidation and infection, such as

Figure 1: Extrahepatic sites of CRP production



cytomegalovirus may trigger a pro-inflammatory cytokine cascade resulting in CRP release.¹⁷ CRP may be secreted from active human peripheral blood monocytes while generation from peripheral blood mononuclear cells (PBMC) is poorly established.^{12, 14, 18} Expression of CRP by human respiratory epithelial cells and alveolar macrophages suggests contribution to bacterial clearance and direct involvement in pulmonary host defense and immune response.^{11, 19} Biosynthetic labeling with S-met and immuno-precipitation with anti-CRP antibodies and *Staphylococcus aureus* indicate that cell surface CRP is produced by lymphocytes.^{11, 20, 21, 35}

Structure of CRP

CRP is a pattern recognition molecule binding to specific molecular configurations that are typically exposed during cell death or found on the surfaces of pathogens. It is a calcium-dependent ligand-binding plasma protein, which is phylogenetically highly conserved with homologues in vertebrates and many invertebrates.¹

Human CRP is a non-glycosylated polypeptide with five identical subunits or protomers.⁵ Each subunit is constituted by 206 amino acid residues and bound to each other by non-covalent bonds.² Structure of CRP based on the amino acid composition, as derived from the sequence data and a minimal molecular weight of 20,946, has been calculated

for human CRP.¹ X-ray crystallography has demonstrated the structure of the protomer (Figure 2) as two antiparallel β -sheets with a flattened jelly-roll topology similar to that of lectins, especially concanavalin.^{1, 6, 7} Each subunit has a recognition face with a phosphocholine binding site consisting of two coordinated calcium ions adjacent to a hydrophobic pocket. Phe-66 and Glu-81 are the two key residues mediating the binding of phosphocholine to CRP. Phe-66 provides hydrophobic interactions with the methyl groups and Glu-81 is found on the opposite end of the pocket where it interacts with the positively charged nitrogen of phosphocholine.¹ The opposite face of the pentamer is the effector face, where complement C1q binds and serves as Fc γ receptors. CRP binding to C1q activates the classical complement pathway up to the level of the C3 convertase. The role of CRP receptors in various processes is mapped in figure 3.

Functions of CRP

CRP, an inducible protein secreted in response to inflammatory stimulus, binds to pathogens and activates the complement to enhance opsonisation and clearance, even before the production of specific IgM or IgG. Involvement of CRP in various immunological processes is mapped in figure 4. CRP bound to a multivalent ligand initiates the assembly of a C3 convertase through classical pathway, which leads to the presentation of ligand with opsonic

Figure 2: Pentameric structure of CRP. Phosphocholine along with the two calcium ions, are located at the binding sites of each promoter (Courtesy: Protein Data Bank)

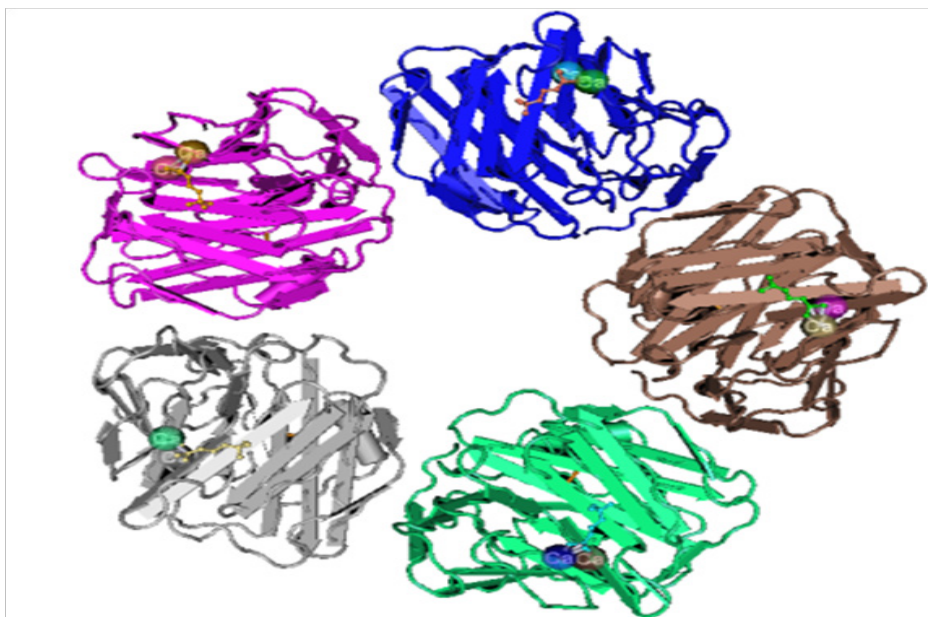


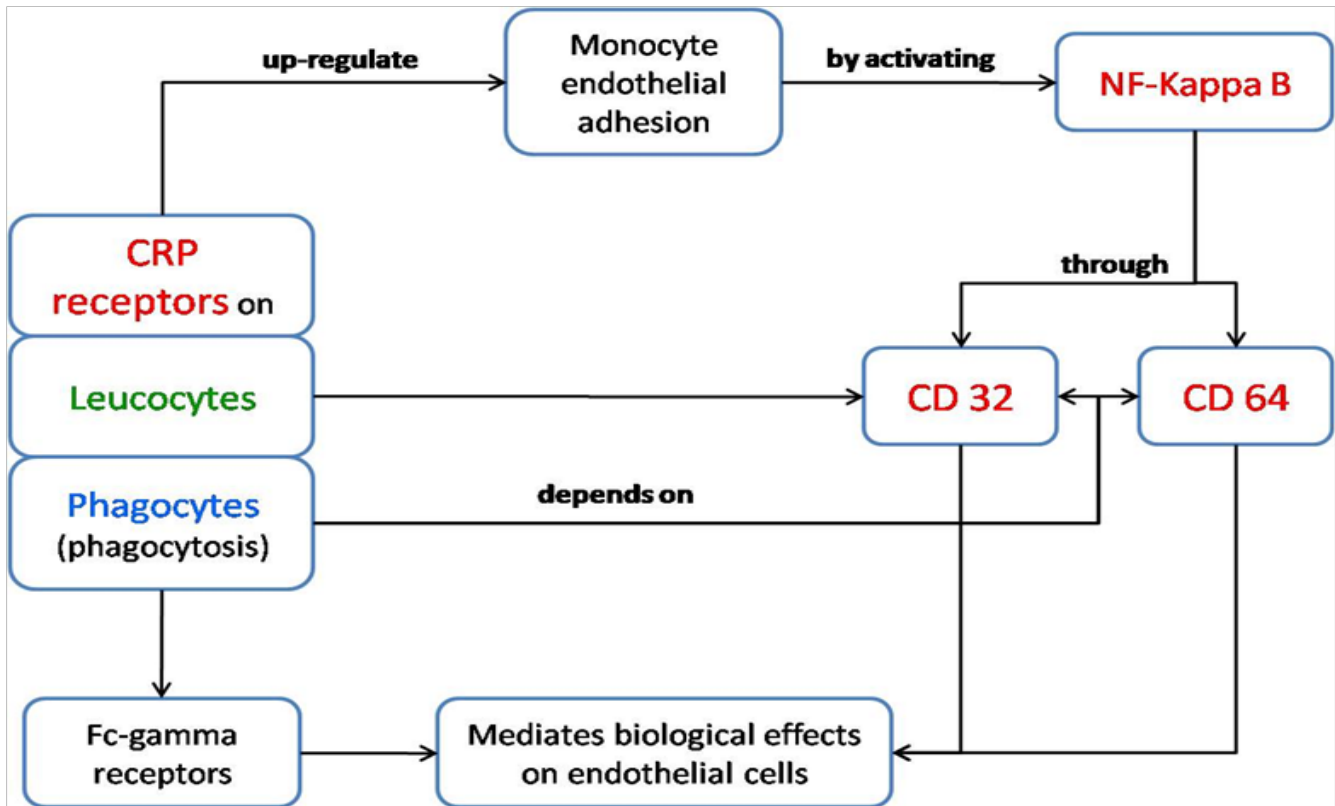
Table 1: Functions of CRP

Binds to bacteria or cells and interacts with the natural killer cells and monocytes, may increase the tumoricidal activity of these cells ^{5, 11}
Activates endothelial cells to express adhesion molecules, chemokines, and cytokines
Inhibits nitric oxide (NO) production and stimulation of nitric oxide release through down regulation of endothelial nitric oxide synthase
Upregulates angiotensin receptor-1 (AT1-R) protein expression, increases AT1-R number on vascular smooth muscle cells, and promotes vascular smooth muscle migration and proliferation <i>in vitro</i>
Serves as chemoattractant for monocytes and induces tissue factor expression in macrophages
Mediates uptake of native LDL into macrophages ^{14, 27}
Activates complement pathway up to C5 convertase and enhances phagocytosis
Amplifies inflammatory responses ^{5, 11}

complement fragments.²² However, the protein does not favor the formation of a C5 convertase and hence, CRP-initiated complement activation does not mediate acute inflammatory reactions and membrane damage.²² The protein has been shown to induce the synthesis of IL-1 α , IL-1 β , TNF- α , and IL-6 in human peripheral blood mononuclear cells and alveolar macrophages.⁵ Furthermore, soluble and immobilized CRPs have been demonstrated to mediate the uptake of native low density lipoprotein (LDL) into macrophages.²³ CRP may also function as a substrate for membrane-associated neutrophil serine protease that

cannot be up-regulated. On the contrary, the degradation of CRP yields small soluble bioactive peptides (Figure 5) that inhibit many of the pro-inflammatory and tissue-destructive potential of neutrophils. These peptides are possibly involved in signal transduction pathways leading to neutrophil activation.⁴ CRP shares major amino acid sequences with SAA fragments. Heat-aggregated CRP has been demonstrated to activate platelet aggregation, secretion, and generation of thromboxane A₂, similar to heat-aggregated IgG. Human SAA seems to selectively modulate platelet reactivity and down-regulate at least

Figure 3: Role of CRP receptors



one aspect of the biologic capacity of its acute-phase homologue, CRP.²⁴

Three of the synthetic peptides corresponding to residues 201-206 (CRP-III), 83-90 (CRP-IV), and 77-82 (CRP-V) of the intact protein were identified to act additively to inhibit superoxide production from activated neutrophils at 50 μ M, whereas CRP-III and CRP-V inhibit neutrophil chemotaxis.^{24, 25} Studies indicate a specific activation-independent action of CRP, CRP peptides (174-185), and CRP-III on the expression of L-selectin. CRP peptides attenuate neutrophil adhesion to the endothelium and consequently neutrophil trafficking into tissues, thereby limiting the inflammatory response.²⁶ Some of the critical functions of CRP are shown in table 1.

Ligand interactions

CRP is the first pattern recognition receptor identified possessing greater affinity to bind to a molecule identified by a specific pattern.²⁸ The ligand binding site of CRP, composed of loops with two calcium ions 4 Å apart and bound by protein side-chains, is located on the concave face.⁵ Phosphocholine (PC), a component in the biological

cell membranes of bacteria and fungi, is the first identified ligand that binds to CRP.^{1,2} Ligands known to bind to CRP are listed in table 2.

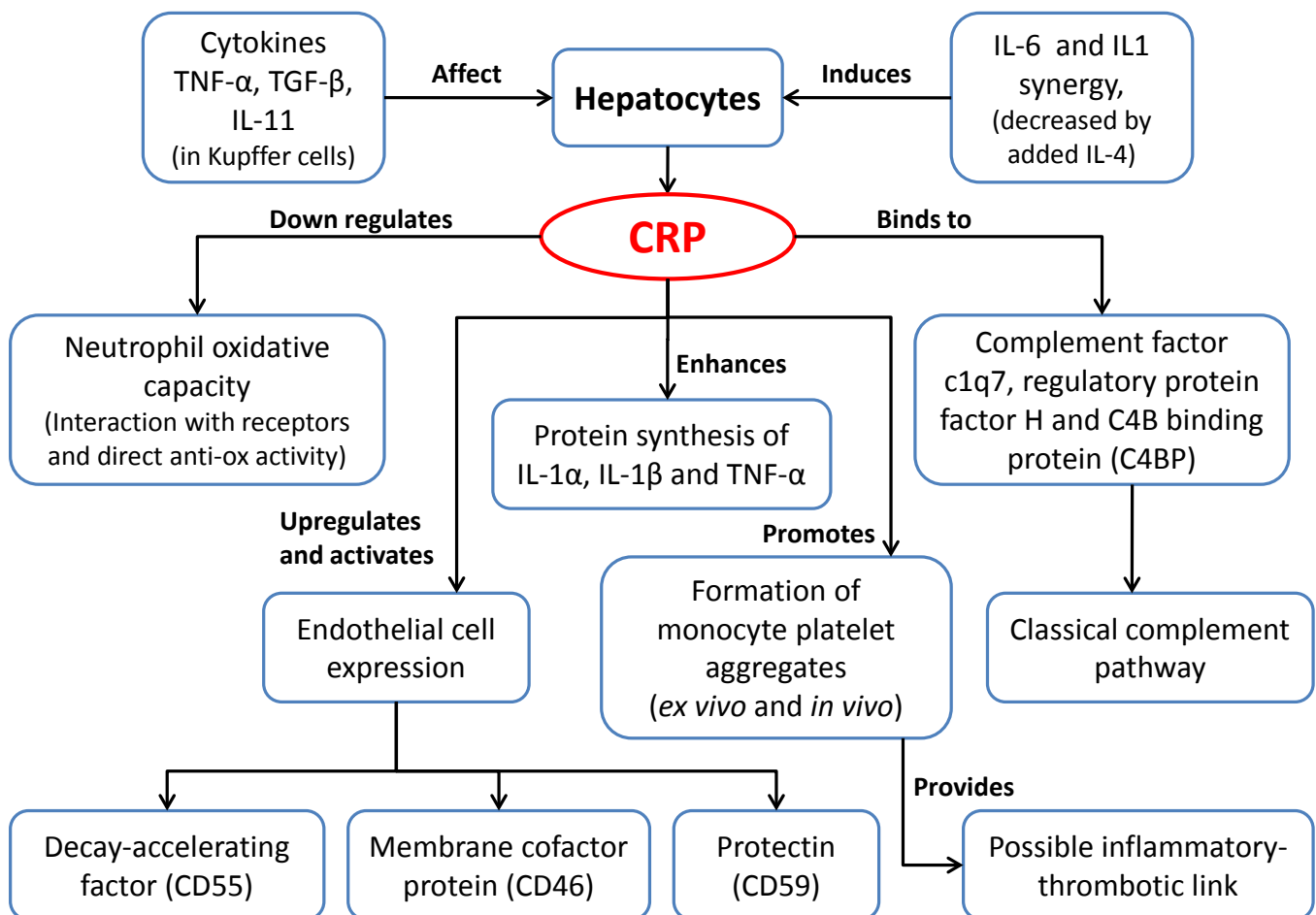
CRP gene regulation

The CRP gene, located on the 1q23.2 on chromosome 1, contains one intron separating the region encoding the signal peptide from that encoding the mature protein.^{1,29} The CRP gene sequence was determined in 1985 simultaneously by two different research teams.^{30,31} The first exon encodes a signal peptide and the first two amino acids of the mature protein. This is followed by a 278-nucleotide-long intron that includes a GT repeat sequence. The second exon encodes the remaining 204 amino acids, followed by a stop codon.³² Goldman et al. has reported for the first time that the GT stretch in the intron is polymorphic in length. Two recent studies describe polymorphisms in the CRP intron gene and promoter that influences the normal expression levels.³³ Individuals with particular allele combinations exhibit two-fold lower baseline CRP levels, perhaps due to DNA structural changes that affect transcription.³³ Within the promoter, several polymorphisms were discovered in transcription factor binding E-box sites, all of which

Table 2: CRP-binding ligands

Autologous ligands include native and modified plasma lipoproteins, damaged cell membranes, different phospholipids and related compounds, small nuclear ribonucleoprotein particles, and apoptotic cells. ^{34, 35, 36}
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.
Macromolecular ligands, phosphoethanolamine, chromatin, histones, fibronectin, small nuclear ribonucleoproteins, laminin, and polycations ^{20, 37}
Phosphocholine esters, polycations and galactans (lectin character) ³⁴
<i>In vitro</i> , human CRP directly inhibits the binding of leptin to its receptors and blocks its ability to signal in cultured cells. Human CRP has been correlated with increased adiposity and plasma leptin. Thus, suggesting a potential mechanism contributing to leptin resistance by which circulating CRP binds to leptin and attenuates its physiological functions. ³⁸
Phosphorylcholine (Ca ²⁺ -dependent binding specificity), lipids (polar head group), lecithin (phosphatidylcholine, PC) and sphingomyelin (SM), and plasma lipoproteins ³⁴
Histones H1 and H2A most strongly and less binding to H2B, H3 and H4, and polycations ³⁷

Figure 4: Involvement of CRP in various processes



resulted in different baseline circulating levels of CRP and response by other genes that encode cytokines affecting its synthesis, such as IL-6, IL-1 and TNF- α .²⁹ Single nucleotide polymorphisms (SNPs) across the CRP gene have been associated with differences in basal CRP levels. CRP gene contains binding sites for STAT3 (transcription factors) and Rel proteins.¹ It is well established that IL-6 stimulates the acute phase expression of CRP.³⁹ Polymorphism in the human CRP gene resulting in a lower basal level of CRP has been associated with an increased risk of developing systemic lupus erythematosus.¹

Different functional forms of CRP

Studies have found different structural forms of CRP (Figure 6), such as, the pentameric ring, globulin and fibril structures, which are observed by combination of size-exclusion chromatography and electron microscopy. Denatured and aggregated forms of CRP (neo-CRP or modified CRP) have been also reported.⁴⁰ The pentameric ring-like CRP was observed mostly on ligand containing membrane in a calcium-dependent manner. The globulin-

like monomers, found on negatively charged membrane in the absence of calcium, exhibit structural stability. The fibril-like structures were formed by face-to-face stacking of a number (several to hundreds) of pentameric CRP. The freshly purified CRP forms short single-strand fibrils while that stored for more than several days form long and bundled fibrils. In 1965, Gotschlich and Edelman reported for the first time that the CRPs purified from serum were mainly pentamers.⁴¹ CRP exists in two distinct forms: (i) native pentameric CRP (nCRP), detectable in serum with both pro- and anti-inflammatory effects, and (ii) the tissue-bound modified or monomeric CRP (mCRP), with predominantly pro-inflammatory effects.⁴²

Native CRP, which exists as a pentamer, dissociates to mCRP due to conformational rearrangement. There is growing evidence that mCRP may have novel pro-inflammatory and thrombotic properties.⁴³ mCRP is found to be deposited in human aortic and carotid atherosclerotic plaques, but not in healthy vessels.⁴⁴ In 1983, Potempa *et al.* reported another type of CRP, termed 'modified CRP',

Figure 5: Degradation products of CRP and their functions

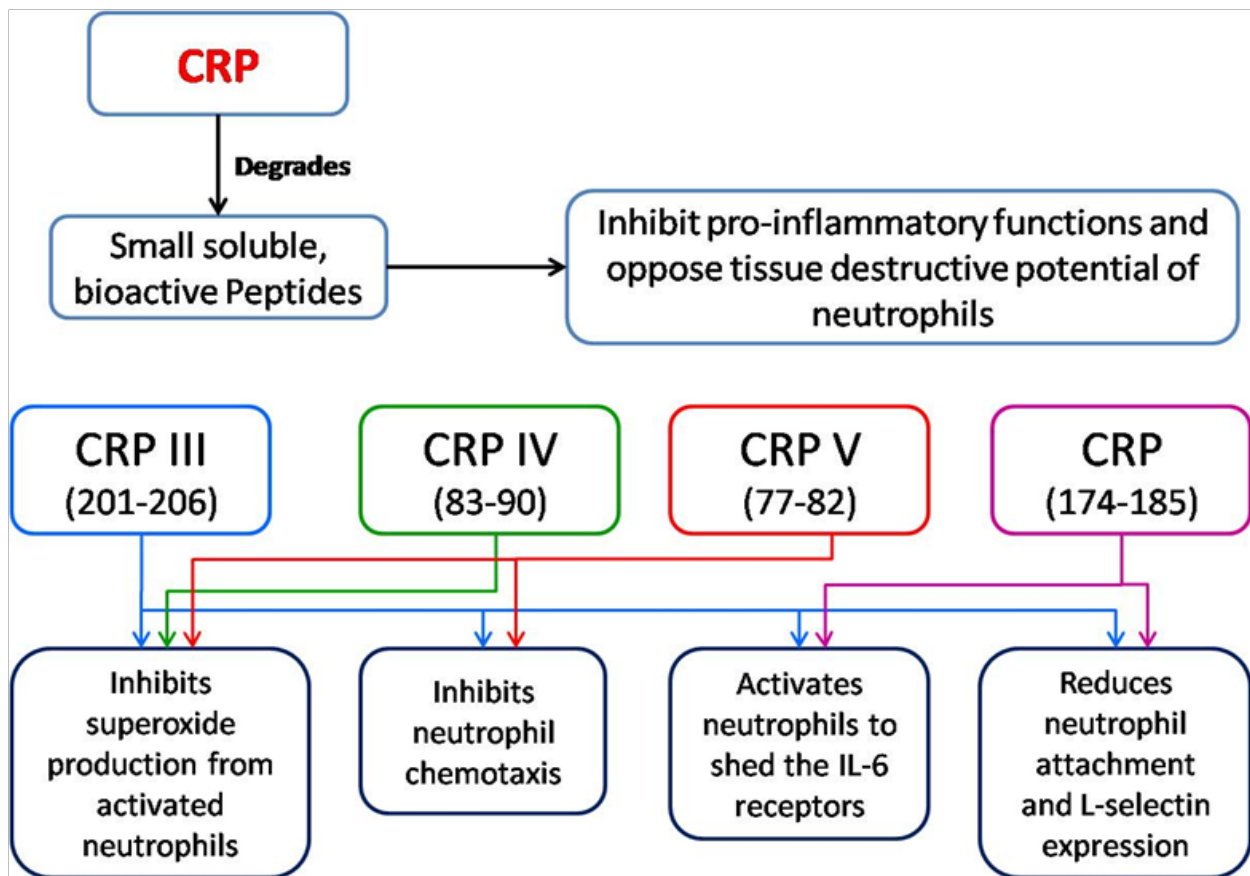
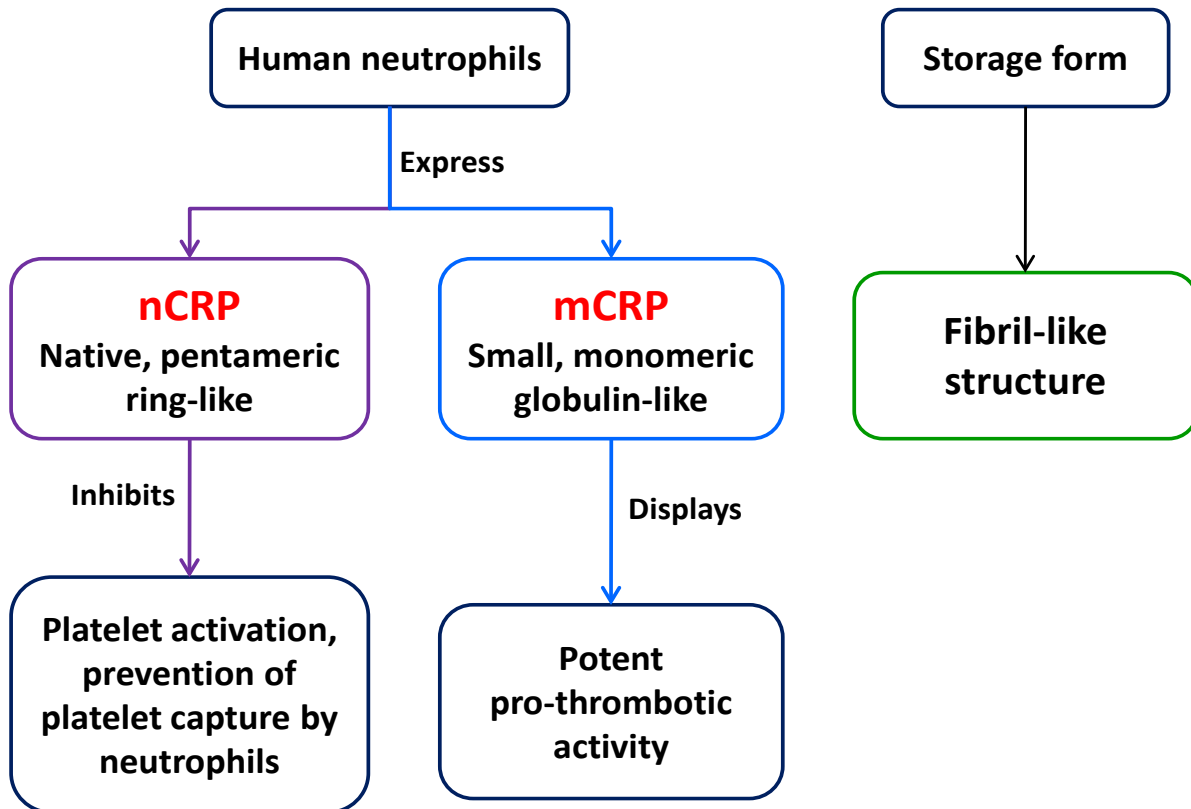


Figure 6: Different forms of CRP and their functions



produced on urea-EDTA or acid-EDTA treatment.⁴⁵ The modified CRP runs faster in gel electrophoresis and has lower solubility than native CRP.⁴⁰ pCRP is formed by urea-chelation treatment and resembles the free subunit mCRP. mCRP has distinct physicochemical, antigenic and biologic activities compared to CRP.⁴⁶ mCRP enhances platelet aggregation and secretion of serotonin, modulation of arachidonic acid metabolism, stimulation of interleukin-1 (IL 1) release, potentiation of the respiratory burst response of human neutrophils, and peripheral blood monocytes to heat modified IgG.⁴ The different structural forms may convert to each other under certain conditions, suggesting structural basis of multiple functions of CRP. Native CRP binds to CD32, whereas mCRP binds to CD16. It was suggested that native CRP dissociated into monomeric units on binding to plasma membrane, or in a denaturing or oxidative environment.^{14,40} mCRP can inhibit as well as activate the classical complement pathway by binding to C1q, depending on its presence in a fluid phase or surface-bound state.⁴⁸ Identification of suitable assays that allow direct testing of mCRP, instead of native CRP in serum or tissue, will further clarify its biological significance.¹⁴

Role of CRP in physiology and pathology

CRP, mainly recognized as a biomarker of inflammation, is now viewed as a direct contributor in atherosclerosis as it functions both as 'pro-inflammatory' and 'anti-inflammatory' molecule.¹ With the advent of high-sensitivity assays for determining CRP, the protein has emerged as one of the most powerful independent predictors of cardiovascular disease. CRP level, which significantly increases in acute coronary syndromes, has a prognostic value in patients with cardiovascular complications and in apparently healthy individuals. The *in vivo* mechanisms of CRP as a mediator of the inflammatory state and thrombotic complications are continuing to be unraveled. Here, we focus on the role of CRP in the pathophysiology of atherosclerosis including the potential mechanisms of action in circulation as well as the potential contribution of genetic variations within the CRP gene.⁴⁹ The capacity of human CRP to activate/regulate complement may be an important characteristic that links CRP and inflammation with atherosclerosis. Recent advances suggest that, in addition to classical pentameric CRP, mCRP may also play an active role in atherosclerosis. The capacity of mCRP to interact and activate the complement cascade is unknown.⁴⁸ Loss

of pentameric symmetry in CRP is associated with the appearance of novel bioactivities in mCRP that enhance neutrophil localization and activation at the inflamed or injured vascular sites.⁵⁰ The biological effect of CRP on the development of atherosclerosis seems to encompass a complex network of interactions with other players in immunity and inflammation, such as the complement system. It may also involve the direct effect of CRP on the cells involved in lesion growth and development.⁵¹ Evidence suggests that CRP functions as a powerful pro-atherogenic factor, in addition to being a risk factor for atherosclerotic and metabolic events. A growing body of evidence implicates CRP as a powerful risk marker for diverse cardiovascular and metabolic diseases. Possibly, it is also a mediator of these diseases as it contributes to the substrate underlying lesion formation, plaque rupture, and coronary thrombosis.^{17, 51}

A CRP mutant incapable of binding to PC provides a tool to assess PC-dependent interactions of CRP with the other biologically significant ligands and to further investigate the functions of CRP in host defense and inflammation.⁵² Findings indicate that CRP can modify the course of autoimmune disease, possibly by preventing the exposure of nuclear antigens to the immune system. A close relationship between leptin and CRP supports the view that the adipokine (leptin) has a possible role in inflammation and atherothrombosis, besides being involved in the pathophysiology of obesity.^{38, 53} Physiological concentrations of leptin can stimulate expression of CRP in human primary hepatocytes. Recently, human CRP has been correlated with increased adiposity and plasma leptin, suggesting that circulating CRP binds to leptin and attenuates its physiological functions. This could be a potential mechanism contributing to leptin resistance.

A growing body of evidence implicates CRP as a direct mediator of endothelial dysfunction.⁵⁴ Patients with elevated levels of CRP have been shown to elicit impaired endothelium-dependent vasodilatation, suggesting that CRP may be a useful clinical tool for endothelial vasomotion.⁵⁵ CRP may also directly promote monocyte activation by stimulating the release of cytokines, such as IL-1b, IL-6, and TNF- α .⁵⁰ Recent evidence shows that CRP is deposited in the arterial intima, at the sites of atherogenesis.^{23, 56} CRP induces up-regulation of adhesion molecules and monocyte chemoattractant protein-1 in venous endothelial cells. CRP is proatherogenic in monocyte/macrophages, because it increases tissue

factor expression, promotes monocyte chemotaxis and adhesion to endothelial cells, release of reactive oxygen species and matrix metalloproteinase-1, and the uptake of oxidized low-density lipoprotein, leading to increased foam cell formation. Furthermore, CRP is present in foam cells in the atherosclerotic lesion and activates complement.^{57, 58}

CRP as a marker of various diseases/conditions

In the absence of inflammation, CRP is not constitutively expressed and its level is undetectable. Baseline concentrations of CRP are influenced by many factors, including chronic microbial infections, smoking, BMI, coffee consumption, oral contraceptive use, and genetics.⁵⁷ Lifestyle factors, such as smoking and BMI, have a greater influence on baseline CRP levels than single nucleotide polymorphisms (SNPs), making the identification of a genetic association of CRP SNPs with cardiovascular diseases difficult.⁵⁹ The level of CRP is altered in variety of conditions; although the rise in CRP is non-specific, the quantum and the pattern of rise will help deduce the diagnosis. A few clinical situations are discussed in the following sections.

CRP during normal pregnancy

CRP does not cross the placental barrier and therefore, will be useful in diagnosing infections in newborns.⁶⁰ Recently, it has been shown that CRP is present in amniotic fluid and fetal urine, and the elevated levels are associated with adverse pregnancy outcome.⁶¹ These results demonstrate that the human placenta produces and releases CRP, like other placental proteins, mainly into the maternal circulation.

CRP and cardiovascular risk

The association between CRP and cardiovascular risk is driven predominantly by systemic inflammation (Table 3). CRP is unlikely to contribute directly to cardiovascular disease as a pathogenic factor. Similar conclusions were drawn from recent Mendelian randomization studies. Using widely available high-sensitivity assays, CRP levels of 1, 1 to 3, and 3 mg/L have been classified as low, moderate, and high-risk groups for future cardiovascular events. Individuals with LDL cholesterol below 130 mg/dL and CRP levels of 3 mg/dL represent a high-risk group. The conversion of plasma CRP (pCRP) to monomeric CRP (mCRP) has been described as being mediated by activated platelets, which are associated with cardiovascular risks.^{3, 44}

Table 3: Cardiovascular diseases

Sl. No.	CRP Levels (mg/L)	Advantages	Disadvantages	References
Coronary heart disease (CHD)				
1	Low risk < 1 Moderate risk 1 -3 High risk > 3	Consistent association with CHD and CVD risk	Limited information for risk prediction, not better than Framingham risk equation	Shah-2009 ⁷¹
2	High risk ≥ 2.5		Associated with significantly higher risk of death and acute myocardial infarction	Sajadieh-2006 ⁷²
3	High-sensitivity CRP (hs-CRP) 0.7 -2.47		hs-CRP increases incremental predictive value of the risk prediction	Schnell-Inderst-2009 ⁷³
4	Hs-CRP: Group 1 < 45 y 6.1 ± 1.2 Group 2 45-65 y 8.4 ± 2.9 Group 3 ≥ 65 y 11.5 ± 3.2	Hs-CRP was positively correlated to severity of coronary artery disease (CAD) only in older groups.	Hs-CRP peak concentrations did not correlate with angiographic findings in the young	Badran-2009 ⁷⁴
5	Hospitalized >3 Baseline ≤ 3	In stable CHD, elevated CRP levels predict hospitalization for heart failure, independent of baseline heart failure, medication use, CHD severity, and subsequent MI events. Abnormal diastolic function in patients with elevated CRP levels.		Williams-2008 ⁷⁵
6	Low 0.47 ± 0.07 High 8.19 ± 1.95	Patients with CAD had augmented vagal heart rate control with behavioral relaxation, but this effect was moderated by the severity of CRP		Nolan-2007 ⁷⁶
7	Low <1.00 Moderate 1–2.99 High ≥3.00 Mean CRP 2.67 in men 2.28 in women	CRP level helps estimate risk for initial cardiovascular events most effectively in persons at intermediate risk for vascular events		Wilson-2008 ⁷⁷
8	Low < 1 Moderate 1-3 High > 3	> 10 associated with increased morbidity and mortality after cardiac surgery Preoperative CRP levels ≤ 3 associated with increased long-term mortality and extended hospital stay in relatively lower-acuity patients undergoing primary, non-emergent coronary artery bypass graft-only surgery.		Perry-2010 ⁷⁸
9	Mean (SD) (mg/dL) Non-cases 2.8 (5.7) CAD cases 3.3 (3.5)	The Women's Health Study (WHS) did not find an association between lipoprotein-associated phospholipase A ₂ (Lp-PLA ₂) mass and cardiovascular disease, although CRP was significantly associated with disease incidence.		Miller-2010 ⁷⁹

Sl. No.	CRP Levels (mg/L)	Advantages	Disadvantages	References
Atherosclerosis				
1	hsCRP Low < 1 Average 1-3 High > 3 > 10 implies active inflammatory process	Strong predictive association between elevated hsCRP levels and future atherothrombotic events (coronary events, stroke and peripheral arterial disease). hsCRP is an independent predictor of diabetes. Serum hsCRP levels may predict outcome after myocardial infarction and infarct size.		Nakou-2010 ⁸⁰
2	Median hs-CRP Acute rupture 3.2 Plaque erosion 2.9 Stable plaque 2.5 Controls 1.4	Significantly elevated in patients with severe coronary artery disease, both with and without acute coronary thrombosis, and correlates with immunohistochemical staining intensity and numbers of thin cap atheroma		Burke-2002 ⁸¹
Hypertension				
1	Case ≥ 2.54 Control = 0.4	Increased CRP was associated with hypertension, cigarette smoking, and insulin resistance in Mongolian patients		Xu-2008 ⁸²
2	Arterial hypertension resistant (RAH): 6.9 ± 5.8 Controlled (CAH): 4.2 ± 4.8	RAH is associated with higher blood levels of complement C3 and CRP		Magen-2008 ⁸³
3		CRP and TNF- α are increased in oxidative stress and endothelial activation		Cottone-2006 ⁸⁶
4		hsCRP level is not a risk factor for hypertension in rural adults > 50 years		Lee-2005 ⁸⁷
Ischemic stroke				
1	Median (mg/dl) Control 2.6 Case 3.6	Multiple-biomarker panel may be useful for stratifying individual's risk of stroke.	The importance of CRP may be less in older adults than in middle-aged populations	Kaplan-2008 ⁸⁸
2	Geometric mean Women 3.7 Men 3.1	CRP is associated with stroke severity and long-term mortality when measured at least 24 hours after onset. Crude association between high CRP and short term functional outcome, which is likely secondary to stroke severity. CRP is an independent predictor of long-term mortality after ischemic stroke.		Idicula-2009 ⁸⁹
3	hs-CRP Median control 1.48 Incident ischemic stroke 2.85 Incident CHD 3.14	Established marker of systemic inflammation intrinsic to atherosclerosis. More potent marker of future ischemic stroke than lipids alone. Concomitant evaluation of lipid levels and hs-CRP may improve risk assessment for stroke as well as CHD.	Weak correlation between hs-CRP and lipid parameters	Everett-2006 ⁹⁰
4	hsCRP > 3 mg/L: risk of MI and all-cause mortality	Modestly associated with myocardial infarction and mortality.	hsCRP was not associated with ischemic stroke. The value of hsCRP may depend on population characteristics such as age and other risk factors.	Elkind-2009 ⁹²
5	HsCRP (median) Pre-stroke 2.2 Post-stroke 6.5 Median 2.5 pre-MI to 13.5 post-MI	hsCRP increases acutely after stroke and MI; whereas Lp-PLA2 mass and activity levels decrease	These changes imply that measurements made soon after stroke and MI are not reflective of pre-stroke levels and may be less reliable for long-term risk stratification	Elkind-2009A ⁹²

Sl. No.	CRP Levels (mg/L)	Advantages	Disadvantages	References
Pulmonary edema/Chronic obstructive pulmonary disease (COPD)				
1	Median (IQR) ALI/ARDS 119 (62-165) CPE 8 (2-42) Mixed population 100 (36-184)	Results indicate that measurement of CRP and brain natriuretic peptide is useful for discriminating acute lung injury (ALI) or acute respiratory distress syndrome (ARDS) from cardiogenic pulmonary edema (CPE).		Komiya-2011 ⁹³
2	COPD patients 8.37+/-1.14 Asthma patients 3.14+/-0.67 Controls 2.39+/-0.59 COPD smokers 8.37+/-1.14 Ex-smokers 3.14+/-0.67 Non-smokers 2.39+/-0.59	Systemic inflammation plays a role in the pathogenesis of COPD and cigarette smoking might influence this inflammation.		Urboniene-2008 ⁹⁴
3	Mild COPD 3.0 (2.0-5.0) Moderate COPD 3.0 (2.0-6.0) Severe COPD 2.0 (2.0-12.0)	COPD patients with high plasma levels of CRP had more impaired energy metabolism, increased disability, and more distress due to respiratory symptoms than patients with normal CRP levels	The relation between serum CRP levels and exercise tolerance is independent of other factors such as age, sex, and smoking history	Garcia-Rio-2010 ⁹⁵
4	With pulmonary hypertension 8.0 Without hypertension 4.4	CRP and ET-1 play a role in the pathogenesis of pulmonary hypertension-associated COPD		Kwon-2010 ⁹⁶
5	Mean (SD) COPD 5.03 (1.51) COPD patients treated with ICS 3.7 (3.0) Not treated 6.3 (3.6) Control: smokers 2.0 (1.0) Non-smokers 2.2 (1.0)	CRP levels are raised in COPD patients without clinically relevant ischaemic heart disease (IHD). CRP may be a systemic marker of the inflammatory process that occurs in patients with COPD.	Independent of cigarette smoking and reduced in patients with COPD using inhaled corticosteroid (ICS)	PintoPlata-2006 ⁹⁷
Other cardiovascular diseases (CVD)				
1	3-10	Demonstrated an association between slightly elevated CRP plasma levels (3-10 µg/ml) and increased risk of developing CVD in apparently healthy individuals. CRP may have a direct role in atherothrombosis		Pandolfi-2005 ⁹⁸
2	With LVH 8.03 (3.22–30.95) Without LVH 3.93 (1.48–9.48)	Independently correlated with left ventricular mass index (LVMI). hs-CRP may be useful to investigate left ventricular hypertrophy (LVH) in lupus nephritis		Shi-2010 ⁹⁹
3	Low 0.3 High ≥ 0.3	High CRP levels indicate higher risk for both for all-cause and CVD-related mortality than subjects with low CRP levels.		Simanek-2011 ¹⁰⁰
4	hsCRP Low-risk <1 Moderate risk 1-3 High-risk >3	CRP appears to play an important direct role in atherothrombosis		Nash-2005 ¹⁰¹
5	Geometric mean (SD) 0.84 (5.52)	In older African-American subjects, higher patient- assigned scores of experience of social discrimination were linked to higher levels of CRP	Additional research needed to determine the association of CRP over time	Lewis-2010 ¹⁰²

Table 4: Cancer

Sl. No.	CRP Levels (mg/L)	Advantages	Disadvantages	References
Cancer				
1	Controls: 3.2 Patients: ≥20	Plasma CRP level is higher in cancer cases than controls. It is a potential marker of increased cancer risk.		Lee-2011 ¹⁰³
2	≤10 median survival of 79 months >10 pre-surgery level - poor survival	Elevated CRP identifies patients with impaired T-lymphocytic response Elevated pre-operative CRP is an independent predictor of poor cancer-specific survival	Associated with significantly higher risk of death and acute myocardial infarction	Crumley-2006 ¹⁰⁴
3	Normal: < = 5 Elevated: > 5		Do not appear to support a positive association between pre-operative CRP with oral squamous cell carcinoma Further examination in pre-cancerous and HPV+ patients with oral squamous cell carcinoma	Kruse-2010 ¹⁰⁵
Colorectal cancer				
1	> 0.5 - defined as positive	Pre-operative CRP is an independent prognostic factor The levels declined postoperatively, although with a lag.		Shiu-2008 ¹⁰⁶
2	hs-CRP: 1.12 - colorectal cancer 1.13 colon cancer 1.06 rectal cancer	hs-CRP concentrations were weakly associated with an increased risk for colorectal cancer		Tsilidis-2008 ¹⁰⁷
3	Colorectal cancer: 1.05 Normal control group: 0.43	CRP level increased in colorectal cancer patients	No significance for disease free and overall survivals	Kwon-2010 ¹⁰⁸
4	Cut-off CRP level: 125	CRP level aid in decision to ensure safe discharge from hospital after elective colorectal surgery. Patients with CRP >125 on the 4th post-operative day should not be discharged		Ortega-Deballon-2010 ¹⁰⁹
Breast cancer				
1	Mean ± SD breast cancer -5.15± 39.55 Normal - 2.86 ± 16.5	Potential for early, high sensitivity detection of breast cancer	Further validation is required	KwonKim-2009 ¹¹⁰

Table 5: Bacterial / viral infection

Sl. No.	CRP Levels (mg/L)	Advantages	Disadvantages	References
Human immunodeficiency disease (HIV)				
1	Baseline conc. <10	High systemic levels of IL-10, CRP and IL-22 in HIV-1C-infected Indian patients are associated with low viral replication in vitro	Lacks immune-modifying actions	Arias-2010 ¹¹¹
2	< 1 low, 1-3 medium, >3 high risk Median CRP HCV- =1.86 HCV+=1.03 HIV+,HCV-=1.78 HIV+,HCV+=1.3	Demonstrated an association of lower serum lipid and CRP levels with hepatitis C virus (HCV) infection HCV status should be assessed as an important correlate of CV risk factors in older men with or at risk for HIV		Floris-moore-2007 ¹¹²
3	Hs-CRP Low risk <1 Average risk 1-3 High risk >3 Median (IQR) 2.94 (0.83,5.53)	hsCRP was elevated and independently associated with body mass index and lipid changes.		Boger-2009 ¹¹³
Infections				
1	Bacterial infections with high CRP > 100 Viral infections with lower CRP < 10 Tuberculosis < 100, varies with the severity of disease	Aids in the diagnosis of infection, especially using radioimmunoassay kits		Shaw-1991 ⁶⁶
Bacterial infections				
1	The best cut-off value 7.18	CRP and serum procalcitonin (PCT) levels to be significantly higher in the infection group than in the autoimmune disease flare group	PCT level had better sensitivity and specificity compared to CRP in distinguishing between bacterial infections and autoimmune disease flares.	Joo-2011 ⁶⁷
2	Cut-off: 12.5 Bacterial CAP median 14.58 range: 0.3-36.6 Pulmonary TB median 5.27 range: 0.2-13.2	High sensitivity and negative predictive value for differentiating pulmonary TB from bacterial community-acquired pneumonia (CAP) Plays a supplementary role in the exclusion of pulmonary TB from bacterial CAP		Kang-2009 ⁶⁸
3	Febrile bact. infections: mean 63.77 mean rate: 3.61 mg/L/hour Non-bacterial febrile illnesses Mean 23.2 mean rate: 0.41 mg/L/hour	CRP and rate of increase in CRP can differentiate between acute bacterial and non-bacterial febrile illnesses, better than CRP alone		Paran-2009 ¹¹⁴

Sl. No.	CRP Levels (mg/L)	Advantages	Disadvantages	References
Viral infections				
1	> 100		High plasma CRP does not reflect the severity of the nephropathia epidemica	Outinen-2010 ¹¹⁵
2	Serum CRP <28 (lower tertile) ≥70 (upper tertile) Median (range) ICU 123 (69 - 184) Non-ICU 40 (20 - 82)	Serum CRP at early emergency department admission of patients presenting with pandemic H1N1 influenza A infection were found to serve as a useful gauge for predicting disease course and assisting in patient management		Zimmerman-2010 ¹¹⁶

Table 6: Inflammatory diseases

Sl. No.	CRP Levels (mg/L)	Advantages	Disadvantages	References
Sepsis				
1	Mild 10.60 Severe 11.70	Serum soluble triggering receptor expressed on myeloid cells-1 (sTREM-1) levels reflect the severity of sepsis more accurately	CRP and procalcitonin are not very sensitive for dynamic evaluation of sepsis	Zhang-2011 ¹¹⁷
Rheumatoid arthritis				
1	sub-acute ≤10 acute >10 Median All = 8.8 Pso = 6.3 RA =12.0 AS = 11.5 PsA = 8.0	CRP may predict all-cause mortality after standardization for traditional risk factors CRP status changed from sub-acute to acute over 1 year		Poole-2009 ¹¹⁸
2	Median ± SE Group 1 (Low <40): 15 ± 10 Group 2 (Intermediate 40-100): 88 ± 20 Group 3 (High >100): 185 ± 93	Low CRP and ESR levels: No radiographic evidence of progression of RA High CRP and ESR levels: deterioration of disease in nearly all patients CRP is a discrete entity and can be measured accurately by immune-diffusion	CRP and ESR levels need to be substantially reduced for at least a year, before any effect could be recognized In patients with variable responses to a drug, even more difficulty in recognizing an effect	Amos-1997 ¹¹⁹
3	< 3 (Normal)	Strong positive correlation between glutamate and erosions in normal CRP patients Higher erosion in patients with higher CRP and estradiol than those with low CRP and high estradiol		Hajati-2009 ⁷⁰

Sl. No.	CRP Levels (mg/L)	Advantages	Disadvantages	References
4	Mean (SD) Abatacept +DMARD: 4.4 (3.6) Placebo + DMARD: 3.5 (3.3) Abatacept + MTX: 3.3 (3.2) Placebo + MTX: 2.5 (2.1) Median hsCRP SLE: 2.3 RA: 5.2 Control: 1.6	CRP and serum procalcitonin (PCT) levels to be significantly higher in the infection group than in the autoimmune disease flare group	PCT level had better sensitivity and specificity compared to CRP in distinguishing bacterial infections and autoimmune disease flares	Wells-2009 ¹²¹
Crohn's disease				
1	High: ≥ 10 Median 53.9 (1 - 228)	CRP, correlated with disease activity in Crohn's disease, can predict moderate and severe disease activity		Karoui-2007 ⁶⁹
Inflammatory bowel disease (IBD)				
1	Median (Range) Standard: < 5 Active: 0.2 (0.007-1.37) Disease: 0.1 (0.01-1.89) High: > 14		hs-CRP not useful to assess disease activity or glucocorticoid treatment in pediatric IBD patients with undetectable CRP	Sidoroff-2010 ¹²²
Systemic lupus erythematosus (SLE)				
1	Median hsCRP SLE: 2.3 RA: 5.2 Control: 1.6	High CRP may contribute independently to atherosclerosis Non-diabetic women have more coronary artery calcification (CAC) than matched controls and may be linked to CRP		Kao-2008 ¹²³
Systemic inflammatory disease				
1	Mean No vasculitis 44.445 Vasculitis 74.953	Used to detect vasculitis. Correlated with plasma levels of CRP		Peters-2009 ¹²⁴

CRP and cancer

CRP levels have been used to predict the risk of cancer, detect cancer recurrence, and in prognosis.⁶² CRP is a biomarker of inflammation and indicator of the immune response to tumors.⁶³ Its role as a predictor of survival has been shown in multiple myeloma, melanoma, lymphoma, ovarian, renal, pancreatic, and gastrointestinal tumors.⁶⁴ Recent evidence has also associated CRP elevation with

the progression of melanoma, ovarian, colorectal and lung cancers, and recurrence of cancer after surgery in certain situations (Table 4).^{64, 65}

CRP and infection

CRP is an important factor in determining the etiology of infection. The level of CRP can be significantly higher in bacterial infections. A value higher than 100mg/L strongly

Table 7: Metabolic syndrome and other diseases

Sl. No.	CRP Levels (mg/L)	Advantages	Disadvantages	References
Metabolic syndrome				
1	hs-CRP >3	Mean log hs-CRP increased as the number of components of metabolic syndrome increased Elevated hs-CRP were 4.6 times higher in obese subjects than in non-obese participants		Huffman-2009 ¹²⁵
2	Case: Mean 3.8 Geo. mean 1.8 Normal: Mean 1.4 Geo. mean 0.4	Majority of children and adolescents with the metabolic syndrome have elevated CRP levels	Possibility of predicting future adverse health events remains to be determined	Ford-2005 ¹²⁶
3	Median CRP Obesity: 0.68 Hypertriglyceridemia: 1.09 Low HDL Cholesterol: 1.93 High blood pressure: 3.01 Abnormal glucose metabolism: 3.88 More than three of the characteristics: 5.75	CRP adds clinically important prognostic information to the metabolic syndrome		Ridker-2003 ¹²⁷
4	Mean ± SD mg/dL Control: 2.90 ± 0.50 Focal fatty liver: 1.70 ± 0.70 NAFLD Steato-hepatitis: 5.20 ± 2.50 Diff. Steatosis: 7.50 ± 1.60	Serum CRP level was increased in non-alcoholic fatty liver disease (NAFLD) compared to controls. CRP can be used as an additional marker for diagnosis of NAFLD		Oruc-2009 ¹²⁸
5	Undetectable < 0.5 mg/dL Detectable 0.5-0.7 mg/dL Elevated ≥ 0.8 mg/dL	In 90+ age group, high CRP associated with increased odds of all-cause dementia, particularly in women		Kravitz-2009 ¹²⁹
6	> 3.3	High CRP associated with prevalent mild cognitive impairment (MCI) and with non-amnesic-MCI in elderly Suggested involvement in the pathogenesis of MCI		Roberts-2009 ¹³⁰
7	Febrile bact. infections: mean 63.77 mean rate: 3.61 mg/L/hour Non-bacterial febrile illnesses mean 23.2 mean rate: 0.41 mg/L/hour	Conditions linked to high CRP and hs-CRP are adiposity, chronic inflammation, metabolic syndrome type 2 diabetes, hypertension, chronic kidney disease, and sleep apnea At equiv. LDL cholesterol-lowering doses, statins significantly reduced hsCRP levels in patients with hyperlipidemia CRP may change the vascular system towards a pro-inflammatory and vasoconstrictive state with increased arterial stiffness, resulting in hypertension		Devaraj-2011 ¹³¹

Table 8: Respiratory disorders

Sl. No.	CRP Levels (mg/L)	Advantages	Disadvantages	References
Bronchial hyperresponsiveness (BHR)				
1	hsCRP 0.20 to 14.5 median: 1.2 Positive test median:1.4 Negative test median: 0.9		Serum hsCRP is not a good marker of BHR, which is mainly dependent on asthmatic inflammation and is measured during bronchial challenge with histamine. This finding is important for interpreting and discussing BHR or local and systemic inflammation	Panaszek-2007 ¹³⁷
Asthma				
2	Lowest levels of hsCRP 0.45 highest quartile 2.21 Range 0.1-70.0 Geometric mean: Asthmatic 1.35 Non-asthmatic 0.96	Non-allergic asthma > non-asthmatic subjects Role of CRP in the pathogenesis of non-allergic asthma could lead to a recognition of new biomarkers hsCRP a risk factor marker for lung diseases; significantly associated with respiratory symptoms and non-allergic asthma, but not allergic asthma	Allergic asthma had levels similar to non-asthmatic subjects	Olafsdottir-2005 ¹³⁸
Upper respiratory tract infection				
3	Median 7-10 Mean 19-24 between day 2 and 3 Moderately elevated CRP 10-60 is more common	Differentiation of bacterial from viral infection: Elevated CRP values: < 7 days: do not support bacterial infection > 7 days: may indicate a viral complication		Melbye-2005 ¹³⁹

suggests bacterial infections, whereas that below 10 mg/L indicates viral infection. In tuberculosis, it is often found to be between 10 to 100 mg/L.⁶⁶ Additional determination of procalcitonin can add specificity in the case of bacterial infections.⁶⁷ The above information is also helpful to distinguish infection from an autoimmune flare. Similarly, the rate of change in CRP levels can differentiate tuberculosis from bacterial pneumonia.⁶⁸

CRP and inflammatory diseases

In the case of inflammatory diseases, CRP level represents the disease activity. Studies have suggested direct correlations of CRP with RA and inflammatory bowel

diseases like Crohn’s disease.^{69, 70} In contrast, in conditions like SLE, CRP is not significantly elevated.

CRP and obesity

CRP concentrations are elevated, predominantly in obese individuals who are insulin resistant, and are in line with the weight loss-associated improvements in insulin resistance. The relation between CRP concentrations and insulin resistance is independent of obesity.⁴⁷

CRP and diabetes

Elevated levels of CRP and IL-6 predict the development of type 2 diabetes. This association supports a possible

Table 9: Chronic diseases

Sl. No.	CRP Levels (mg/L)	Advantages	Disadvantages	References
Chronic kidney disease (CKD)				
1	Low < 8 Medium: 8-10.5 High > 10.5	CRP predicts cardiovascular events and morbidity in CKD stage 3-5 patients, before initiation of chronic hemodialysis		Soriano-2007 ¹⁴⁰
2	Patients: Mean ± SD 14.3 ± 11.4 (> 6 mg/L)	High CRP values indicate a high degree of inflammation in pre-dialysis patients		Abraham-2009 ¹⁴¹
3	High CRP level (>0.6 mg/dL)	CRP is independently associated with serum albumin level and CVD prevalence. Inflammation may be involved in the pathophysiological state of malnutrition and CVD in the early non-diabetic kidney disease	Glomerular filtration rate (GFR) level does not appear to influence CRP level in the earlier stages of CKD	Menon-2003 ¹⁴²
1	Low CRP < 3.0 High CRP ≥ 3.0	High CRP, low albumins provide prognostic information independent of each other in CKD 3-4. Both are independent risk factors for all-cause mortality. High CRP, but not serum albumin, is a risk factor for cardiovascular mortality.		Menon-2005 ¹⁴³
Chronic rheumatic valve disease				
1	Patients 0.62 ± 0.64 Patients with prosthetic valve(s) 0.35 ± 0.41 Healthy subjects 0.24 ± 0.18	Hs-CRP is increased in chronic rheumatic heart disease (P <0.01 and P <0.001 respectively) Inflammatory response still persists in the chronic phase		Golbasi-2002 ¹⁴⁴
Alzheimer's disease				
1	2.5 ± 4.5 (0.1–34.6)	Low Hs-CRP was associated with a significantly more rapid cognitive decline and functional decline relative to higher levels.	Published studies tend to show the opposite; that is, high hsCRP levels were associated with cognitive decline The effects of hsCRP can be confounded by medications (NSAIDs and statins)	Locascio-2008 ¹⁴⁵

role for inflammation in diabetogenesis. CRP is a powerful independent predictor of diabetes, after adjustment for obesity, clinical risk factors, and fasting insulin levels.⁴⁸

Minor increase in CRP level has also been reported to be associated with a number of medical conditions that do not appear to be associated with inflammation. Elevated CRP

is also observed with several genetic polymorphisms of the CRP and other genes, ethnicity, dietary patterns and obesity.¹

Conclusion

CRP is a valuable inflammatory biomarker in various clinical conditions. However, being non-specific, its use is limited. Concomitant occurrence of multiple stimuli of inflammation, and influence of factors other than inflammation, like smoking, obesity and physical stress, reduce the specificity of CRP significantly. In view of these, guidelines are necessary to interpret the CRP levels in a clinical context. Standardization of measurement techniques and reporting should improve the utility of CRP in regular clinical practice.

Competing interests

The authors declare that they have no competing interests.

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