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.\(^\text{1}\) The plasma half-life of CRP is about 19 hours and is constant under all conditions of health and disease.\(^\text{2, 3}\) 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.\(^\text{2, 4}\) 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.\(^\text{5}\) 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.\(^\text{5}\) 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.\(^\text{6, 7}\) Volanakis and Kaplan later identified the specific ligands that bind to CRP.\(^\text{8}\) 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.\(^\text{9}\) 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-1β, 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.\(^\text{1, 10, 11}\) Studies have shown that epithelial cells of both respiratory tract and renal epithelium can also produce CRP under certain circumstances.\(^\text{12, 13}\) Recent studies have demonstrated that human coronary artery smooth muscle cells could also synthesize CRP upon stimulation by inflammatory cytokines.\(^\text{14, 15}\) 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.\(^\text{16}\) Additionally, there is evidence to suggest that lipid peroxidation and infection, such as
Cytomegalovirus may trigger a pro-inflammatory cytokine cascade resulting in CRP release.\(^1\) 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 \(\beta\)-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 Fcγ 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

| Function                                                                                                                                   |
|---------------------------------------------------------------------------------------------------------------------------------------------|
| Binds to bacteria or cells and interacts with the natural killer cells and monocytes, may increase the tumoricidal activity of these cells      |
| 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 in vitro                                                                                           |
| Serves as chemoattractant for monocytes and induces tissue factor expression in macrophages                                                   |
| Mediates uptake of native LDL into macrophages                                                                                            |
| Activates complement pathway up to C5 convertase and enhances phagocytosis                                                                |
| Amplifies inflammatory responses                                                                                                           |

complement fragments. 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. The protein has been shown to induce the synthesis of IL-1α, IL-1β, TNF-α, and IL-6 in human peripheral blood mononuclear cells and alveolar macrophages. Furthermore, soluble and immobilized CRPs have been demonstrated to mediate the uptake of native low density lipoprotein (LDL) into macrophages. 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. 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
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 µM, whereas CRP-III and CRP-V inhibit neutrophil chemotaxis.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{5} Phosphocholine (PC), a component in the biological cell membranes of bacteria and fungi, is the first identified ligand that binds to CRP.\textsuperscript{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.\textsuperscript{1, 29} The CRP gene sequence was determined in 1985 simultaneously by two different research teams.\textsuperscript{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.\textsuperscript{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.\textsuperscript{33} Individuals with particular allele combinations exhibit two-fold lower baseline CRP levels, perhaps due to DNA structural changes that affect transcription.\textsuperscript{33} Within the promoter, several polymorphisms were discovered in transcription factor binding E-box sites, all of which
Autologous ligands include native and modified plasma lipoproteins, damaged cell membranes, different phospholipids and related compounds, small nuclear ribonucleoprotein particles, and apoptotic cells.\textsuperscript{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\textsuperscript{20, 37}

Phosphocholine esters, polycations and galactans (lectin character)\textsuperscript{34}

*In vitro*, 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.\textsuperscript{38}

Histones H1 and H2A most strongly and less binding to H2B, H3 and H4, and polycations\textsuperscript{37}

| 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. |
| **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** | Include phosphoethanolamine, chromatin, histones, fibronectin, small nuclear ribonucleoproteins, laminin, and polycations. |
| **Phosphocholine esters** | Include polycations and galactans (lectin character). |

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Histones H1 and H2A most strongly and less binding to H2B, H3 and H4, and polycations\textsuperscript{37}
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. 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. It is well established that IL-6 stimulates the acute phase expression of CRP. 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.

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. 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. 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.

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. mCRP is found to be deposited in human aortic and carotid atherosclerotic plaques, but not in healthy vessels. In 1983, Potempa et al. reported another type of CRP, termed ‘modified CRP’,...
produced on urea-EDTA or acid-EDTA treatment.\textsuperscript{45} The modified CRP runs faster in gel electrophoresis and has lower solubility than native CRP.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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 \textit{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{51} Evidence suggests that CRP functions as a powerful proatherogenic 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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 eliciting impaired endothelial function. CRP may also directly promote monocyte activation by stimulating the release of cytokines, such as IL-1\textsubscript{b}, IL-6, and TNF-\alpha.\textsuperscript{55} Recent evidence shows that CRP is deposited in the arterial intima, at the sites of atherogenesis.\textsuperscript{23, 54} 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{59} The level of CRP is altered in a 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{3, 44}
| Sl. No. | CRP Levels (mg/L) | Advantages | Disadvantages | References |
|--------|------------------|------------|---------------|------------|
| **Coronary heart disease (CHD)** |                     |            |               |            |
| 1      | Low risk < 1     | Consistent association with CHD and CVD risk | Limited information for risk prediction, not better than Framingham risk equation | Shah-200971 |
|        | Moderate risk 1-3|           |               |            |
|        | High risk > 3    |           |               |            |
| 2      | High risk ≥ 2.5  | Associated with significantly higher risk of death and acute myocardial infarction | Sajadieh-200672 |
| 3      | High-sensitivity CRP (hs-CRP) 0.7 -2.47 | hs-CRP increases incremental predictive value of the risk prediction | Schnell-Inderst-200973 |
| 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. | Badran-200974 |
| 5      | Hospitalized >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-200875 |
|        | Baseline <or= 3  |           |               |            |
| 6      | Low 0.47 ± 0.07  | Patients with CAD had augmented vagal heart rate control with behavioral relaxation, but this effect was moderated by the severity of CRP | Nolan-200776 |
|        | High 8.19 ± 1.95 |           |               |            |
| 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-200877 |
| 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-201078 |
| 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 A2 (Lp-PLA2) mass and cardiovascular disease, although CRP was significantly associated with disease incidence. | Miller-201079 |
| 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<sup>80</sup> |
| 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<sup>81</sup> |
| **Hypertension** | | | | |
| 1 | Case >or=2.54  
Control=0.4 | Increased CRP was associated with hypertension, cigarette smoking, and insulin resistance in Mongolian patients | | Xu-2008<sup>82</sup> |
| 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<sup>83</sup> |
| 3 | CRP and TNF-α are increased in oxidative stress and endothelial activation | | Cottone-2006<sup>86</sup> |
| 4 | hsCRP level is not a risk factor for hypertension in rural adults > 50 years | | Lee-2005<sup>87</sup> |
| **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<sup>88</sup> |
| 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<sup>89</sup> |
| 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. | | Everett-2006<sup>90</sup> |
| 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<sup>92</sup> |
| 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<sup>92</sup> |
| Sl. No. | CRP Levels (mg/L) | Advantages | Disadvantages | References |
|--------|-------------------|------------|---------------|------------|
| 1      | Pulmonary edema/Chronic obstructive pulmonary disease (COPD) | 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<sup>93</sup> |
| 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<sup>94</sup> |
| 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<sup>95</sup> |
| 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<sup>96</sup> |
| 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<sup>97</sup> |

### Other cardiovascular diseases (CVD)

| Sl. No. | CRP Levels (mg/L) | Advantages | Disadvantages | References |
|--------|-------------------|------------|---------------|------------|
| 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<sup>98</sup> |
| 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 hypertropy (LVH) in lupus nephritis | | Shi-2010<sup>99</sup> |
| 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<sup>100</sup> |
| 4      | hsCRP Low-risk <1 Moderate risk 1-3 High-risk >3 | CRP appears to play an important direct role in atherothrombosis | | Nash-2005<sup>101</sup> |
| 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<sup>102</sup> |
| 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<sup>103</sup> |
| 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<sup>104</sup> |
| 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<sup>105</sup> |
| **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<sup>106</sup> |
| 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 | | Tsiliidis-2008<sup>107</sup> |
| 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<sup>108</sup> |
| 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<sup>109</sup> |
| **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<sup>110</sup> |
| Sl. No. | CRP Levels (mg/L) | Advantages | Disadvantages | References |
|--------|-------------------|------------|--------------|------------|
| 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 | 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

| Sl. No. | CRP Levels (mg/L) | Advantages | Disadvantages | References |
|--------|-------------------|------------|--------------|------------|
| 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[^56] |
| 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] |

[^56]: Shaw-1991[^56]
[^68]: Kang-2009[^68]
[^111]: Arias-2010[^111]
[^112]: Floris-moore-2007[^112]
[^113]: Boger-2009[^113]
[^114]: Paran-2009[^114]
### Viral infections

| Sl. No. | CRP Levels (mg/L) | Advantages                                      | Disadvantages                                      | References            |
|---------|-------------------|------------------------------------------------|---------------------------------------------------|-----------------------|
| 1       | > 100             | High plasma CRP does not reflect the severity of the nephropathia epidemica |                                                    | Outinen-2010<sup>115</sup> |
| 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<sup>116</sup> |

### Table 6: Inflammatory diseases

| Sl. No. | CRP Levels (mg/L) | Advantages                                      | Disadvantages                                      | References            |
|---------|-------------------|------------------------------------------------|---------------------------------------------------|-----------------------|
| 1       | Mild 10.60        | 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<sup>117</sup> |
|         | Severe 11.70      |                                                |                                                   |                       |
| 1       | sub-acute ≤10 acute >10 | 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<sup>118</sup> |
|         | Median All = 8.8  |                                                |                                                   |                       |
|         | Pso = 6.3         |                                                |                                                   |                       |
|         | RA =12.0          |                                                |                                                   |                       |
|         | AS = 11.5         |                                                |                                                   |                       |
|         | PsA = 8.0         |                                                |                                                   |                       |
| 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<sup>119</sup> |
| 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<sup>70</sup> |
| Sl. No. | CRP Levels (mg/L) | Advantages | Disadvantages | References |
|--------|-------------------|------------|---------------|------------|
| 4      | Mean (SD)         | 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-2009121 |
|        | 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 | | | |

**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-200799 |

**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-2010122 |

**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-2008123 |

**Systemic inflammatory disease**

| 1 | Mean No vasculitis 44.445 Vasculitis 74.953 | Used to detect vasculitis. Correlated with plasma levels of CRP | Peters-2009124 |

**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
| Sl. No. | CRP Levels (mg/L) | Advantages | Disadvantages | References |
|--------|-------------------|------------|---------------|------------|
| 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    | 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\(^{126}\) |
|        | Geo. mean 1.8    |                         |               |            |
|        | Normal: Mean 1.4 |                         |               |            |
|        | Geo. mean 0.4    |                         |               |            |
| 3      | Median CRP       | CRP adds clinically important prognostic information to the metabolic syndrome |  | Ridker-2003\(^{127}\) |
|        | 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 | | | |
| 4      | Mean ± SD mg/dL  | 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\(^{128}\) |
|        | 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 | | | |
| 5      | Undetectable     | In 90+ age group, high CRP associated with increased odds of all-cause dementia, particularly in women |  | Kravitz-2009\(^{129}\) |
|        | < 0.5 mg/dL      |                         |               |            |
|        | Detectable       |                         |               |            |
|        | 0.5-0.7 mg/dL    |                         |               |            |
|        | Elevated         |                         |               |            |
|        | ≥ 0.8 mg/dL      |                         |               |            |
| 6      | > 3.3            | High CRP associated with prevalent mild cognitive impairment (MCI) and with non-amnestic-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 7: Metabolic syndrome and other diseases
Table 8: Respiratory disorders

| Sl. No. | CRP Levels (mg/L) | Advantages | Disadvantages | References |
|---------|------------------|------------|--------------|------------|
| 1       | 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\textsuperscript{137} |
| 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\textsuperscript{138} |
| 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\textsuperscript{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.\textsuperscript{66} Additional determination of procalcitonin can add specificity in the case of bacterial infections.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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<sup>140</sup> |
| 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<sup>141</sup> |
| 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<sup>142</sup> |
| **Chronic rheumatic valve disease** | | | | Golbasi-2002<sup>144</sup> |
| 1 | Patients 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 | | | |
| | 0.62 ± 0.64 Patients with prosthetic valve(s) 0.35 ± 0.41 Healthy subjects 0.24 ± 0.18 | | | |
| **Alzheimer’s disease** | | | | Locascio-2008<sup>146</sup> |
| 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) | |

Role for inflammation in diabetogenesis. CRP is a powerful independent predictor of diabetes, after adjustment for obesity, clinical risk factors, and fasting insulin levels. 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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References
1. Pepys MB and Hirschfield GM. C-reactive protein: a critical update. J Clin Invest 2003;111(12).
2. Black S, Kushner I, Samols D. C-reactive protein. J BiolChem 2004;279:48487-48490.
3. Ying SC, Marchalonis JJ, Gewurz AT, Siegel JN, Jiang H, Gewurz RE, et al. Reactivity of anti-human C-reactive protein (CRP) and serum amyloid P component (SAP) monoclonal antibodies with limulin and pentraxins of other species. Immunology 1992;76(2):324-330.
4. Pepys MB and Baltz ML. Acute phase proteins with special reference to C-reactive protein and related proteins (pentaxins) and serum amyloid A protein. AdvImmunol 1983;34:141-212.
5. Tillett WS and Francis T Jr. Serological reactions in pneumonia with a non-protein somatic fraction of pneumococcus. J Exp Med 1930;52:561-571.
6. Macleod C and 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;73:183-190.
7. 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;85:491-498.
8. Volanakis JE and Kaplan MH. Specificity of C-reactive protein for choline phosphate residues of pneumococcal C-polysaccharide. ProcSocExpBiol Med 1971;136:612-614.
9. Clyne B, Olshaker JS. The C-reactive protein. J Emerg Med 1999;17(6):1019-1025.
10. Jialal I, Devaraj S, Venugopalk S. C-reactive protein: risk marker or mediator in atherothrombosis? Hypertension 2004;44(1):6-11.
11. Kuta AE and Baum LL. C-reactive protein is produced by a small number of normal human peripheral blood lymphocytes. J ExpMed 1986;164:321-326.
12. Gould JM and Weiser JN. Expression of C-reactive protein in the human respiratory tract. Infect Immun 2001;69(3):1747-1754.
13. Logering BA, Gerke P, Kreft B, Wolber EM, Klinger MH, Fricke L, et al. The kidney as a second site of human C-reactive protein formation in vivo. Euro J Immunol 2003;33:152-161.
14. Yeh ETH. A new perspective on the biology of C-reactive protein. Circul Res 2005;97:609.
15. Calabro P, Willerson JT, Yeh ETH. Inflammatory cytokines stimulated C-reactive protein production by human coronary artery smooth muscle cells. Circulation 2003;108:1930.
16. Venugopalk S, Devaraj S, Jialal I. Macrophage conditioned medium induces the expression of C-reactive protein in human aortic endothelial cells. Potential for paracrine/autocrine effects. Am J Pathol 2005;166(4):1265-1271.
17. Verma S and Yeh ETH. C-reactive protein and atherothrombosis—Beyond a biomarker: an actual partaker of lesion formation. Am J PhysiolRegulIntegr Comp Physiol 2003; 285:R1253–R1256.
18. Barma BP, James K, Deodhar SD. Activation of human monocyte tumouricidal activity by C-reactive protein. Cancer Res 1987;47(15):3959-3963.
19. Fiedel BA, Ku CS, Izz J, Gewurz H. Selective inhibition of platelet activation by the amyloid P-component of serum. J Immunol 1983;131(3):1416-1419.
20. Szalai AJ, Agrawal A, Greenough TJ, Volanakis JE. C-reactive protein: structural biology and host defense function. ClinChem Lab Med. 1999;37(3):265-270.
21. Dong Q, Wright JR. Expression of C-reactive protein by alveolar macrophages. J Immunol 1996;156(12):4815-4820.
22. J E Volanakis. Human C-reactive protein: expression, structure, and function. MolImmunol 2001.
23. Smitha CN, Soni S, Basu SK. Role of C-reactive protein and periodontal disease in systemic health: A review. J Adv Dent Res 2011;2(1):1-5.
24. Shephard EG, Anderson O, Rosen O, Myer MS, Frdrk M, Strachan AF, et al. Peptides generated from C-reactive protein by a neutrophil membrane protease. Amino acid sequence and effects of peptides on neutrophil oxidative metabolism and chemotaxis. J Immunol 1999;165(5):1469-1476.
25. Zouki C, Beauchamp M, Baron C, Filep JG. Prevention of in vitro neutrophil adhesion to endothelial cells through shedding of L-selectin by C-reactive protein and peptides derived from C-reactive protein. J Clin Invest 1997;100(3):522-529.
26. Zouki C, Haas B, Chan JS, Potema LA, Filep JG. Loss of pentamer symmetry of C-reactive protein is associated with promotion of neutrophil-endothelial cell adhesion. J Immunol 2001;167(9):5355-5361.
27. Blake GJ and Ridker PM. C-reactive protein: a surrogate risk marker or mediator of atherothrombosis? Am J Physiol Renal Physiol 2003;285.
28. Deban L, Bottazzi B, Garlanda C, de la Torre YM, Mantovani A. Pentraxins: multifunctional proteins at the interface of innate immunity and inflammation. Biofactors 2009;35(2):138-145.
29. Hage FG and Szalai AJ. The role of C-reactive protein polymorphisms in inflammation and cardiovascular risk. CurrAtheroscler Reps 2009;11(2):124-130.
30. Woo P, Korenberg JR, Whitehead AS. Characterization of genomic
and complementary DNA sequence of human C-reactive protein, and comparison with the complementary DNA sequence of serum amyloid P component. J Biol Chem 1985;260:13384-13388.

31. Lei KJ, Liu T, Zon G, Soravia E, Liu TY, Goldman ND. Genomic DNA sequence for human C-reactive protein. J Biol Chem 1985;260:13377-13383.

32. Goldman ND, Liu T, Lei KJ. Structural analysis of the locus containing the human C-reactive protein gene and its related pseudogene. J Biol Chem 1987;262:7001-7005.

33. Szalai AJ, Wu J, Lange EM, McCrory MA, Langefeld, Williams A, et al. Single-nucleotide polymorphisms in the C-reactive protein (CRP) gene promoter that affect transcription factor binding, alter transcriptional activity, and associate with differences in baseline serum CRP level. J Mol Med 2005;83(6):440-447.

34. Sölter J, Uhlenbruck G. The biological importance of C-reactive proteins in non-specific defense mechanisms. Immuninfekt 1982;10(4):130-135.

35. Du Clos TW. C-reactive protein reacts with the U1 small nuclear ribonucleoprotein. J Immunol 1989;143:2553-2559.

36. Gershov D, Kim S, Brot N, Elkon K.B. C-reactive protein binds to apoptotic cells, protects the cells from assembly of the terminal complement components, and sustains an anti-inflammatory innate immune response: implications for systemic autoimmunity. J. Exp Med 2000;192:1353-1363.

37. Black S, Agrawal A, Samols D. The phosphocholine and the polycation-binding sites on rabbit C-reactive protein are structurally and functionally distinct. Mol Immunol 2003;39(16):1045-1054.

38. De Rosa S, Cirillo P, Pacileo M, Di Palma V, Paglia A, ChiarilliOM. Leptin stimulated C-reactive protein production by human coronary artery endothelial cells. J Vasc Res 2009;46(6):609-617. Epub 2009 Jun 30.

39. Agrawal A, Simpson MJ, Black S, Carey MP, Samols D. C-reactive protein mutant that does not bind to phosphocholine and pneumococcal C-polysaccharide. J Immunol 2002;169(6):3217-3222.

40. Wang HW, Wu Y, Chen Y, Sui SF. Polymorphism of structural forms of C-reactive protein. Int J Mol Med 2002;9(6):665-671.

41. Gotschlich EC and Edelman GM. C-reactive protein:a molecule composed of subunits. Proc Natl Acad Sci USA 1965;54:558-562.

42. Schwedler SB, Filep JG, Galle J, Wanner C, Potempa LA. C-reactive protein: a family of proteins to regulate cardiovascular function. Am J Kidney Dis. 2006;47(2):212-222.

43. Habersenber ger, Eisenhower ST, KarlheinzP. C-reactive protein measurement and cardiovascular disease. The Lancet 2010;375(9720):1078.

44. Eisenhower ST, Habersenberger J, Murphy A, Chen YC, Woollard KJ, Bassler N, et al. Dissociation of pentameric to monomeric C-reactive protein on activated platelets localizes inflammation to atherosclerotic plaques. Circ Res 2009;105(2):128-137.

45. Potempa LA, Maldonado BA, Laurent P, Zemel ES, Gewurz H. Antigenic, electrophoretic and binding alterations of human C-reactive protein modified selectively in the absence of calcium. Mol Immunol 1983;20(11):1165-1175.

46. Kresl JJ, Potempa LA, Anderson BE. Conversion of native oligomeric to a modified monomeric form of human C-reactive protein. Int J Biochem Cell Biol 1998;30(12):1415-1426.

47. McLaughlin T, Abbasi F, Lamendola C, Liang L, Reaven G, Schaaf P, et al. Differentiation between obesity and insulin resistance in the association with C-reactive protein. Circulation 2002;106:2908-2912.

48. Ji SR, Wu Y, Potempa LA, Liang YH, Zhao J. Effect of modified C-reactive protein on complement activation: a possible complement regulatory role of modified or monomeric C-reactive protein in atherosclerotic lesions. ArteriosclerThrombVascBiol 2006;26(4):935-941.

49. Boncker M, Luzak B, Watala C. Role of C-reactive protein in atherogenesis. PostepyHig Med Dosw 2006;60:538-546.

50. Jones SA, Novick D, Horuchi S, Yamamoto N, Szalai AJ, Fuller GM. C-reactive protein: a physiological activator of interleukin 6 receptor shedding. J Exp Med 1999;189(3):599-604.

51. Paul A1, Yeh ET, Chan L. A proatherogenic role for C-reactive protein in vivo. CurrOpinLipidol 2005;16(5):512-517.

52. Potempa LA, Siegel JN, Gewurzh. Binding reactivity of C-reactive protein for polycations. II. Modulatory effects of calcium and phosphocholine. J Immunol 1981;127(4):1509-1514.

53. Di Napoli M, Schwaninger M, Cappelli R, Ceccarelli E, Di Gianfipillo G, Donati C, et al. Evaluation of C-reactive protein measurement for assessing the risk and prognosis in ischemic stroke: A statement for healthcare professionals from the CRP pooling project members. Stroke 2005;36:1316-1329.

54. Verma S, Wang C-H, Li S-H, Dumont AS, Fedak PW, Badiwala MV, et al. A self-fuelling prophecy: C-reactive protein attenuates nitric oxide production and inhibits angiogenesis. Circulation 2002, 106:913-919.

55. Ballou SP, Lozanski G. Induction of inflammatory cytokine release from cultured human monocytes by C-reactive protein. Cytokine 1992;4(5):361-368.

56. Torzewski M, Rist C, Mortensen RF, Zwaka TP, Bieneck M, Waltenberger J, et al. C-reactive protein in the arterial intima: role of C-reactive protein receptor-dependent monocyte recruitment in atherogenesis. ArteriosclerThrombVasc Biol. 2000;20(9):2094-2099.

57. Peisajovich A, Marrell M, Mold C and DuClos TW. C-reactive protein at the interface between innate immunity and inflammation. Expert Rev Clin Immunol 2008;4(3):379-390.

58. Dreon DM, Slavín JL, Phinney SD. Oral contraceptive use and increased plasma concentration of C-reactive protein. Life Science 2003; 73(10):1245-1252.

59. Lakka HM, Lakka TA, Rankinen T et al. The TNF-α G-308A polymorphism is associated with C-reactive protein levels: the HERITAGE Family Study. Vascular Pharmacology 2006;44(5):377-383.

60. Nielsen FR, MøllerBek K, Rasmussen PE, Qvist I, Tobiassen M. CRP does not cross the placental barrier, and may therefore be useful in diagnosing infections in newborns. Biochem 2007; 40(5-6): 330-335.

61. Malek A, Bersinger NA, Di Santo S, Mueller MD, Sager R, Schneider H, et al. C-reactive protein production in term human placental tissue. Placenta 2006; 27(6-7): 619-625.

62. Coventry BJ, Ashdown ML, Quinn MA, Markovic SN, Yatomi-Clarke H, et al. C-reactive protein production in term human placental tissue. Placenta 2006; 27(6-7): 619-625.

63. Groblewska M, Mroczko B, Wereszczyńska-Siemiatkowska U, Kedra B, Lukaszewicz M, Baniukiewicz A, et al. Serum interleukin 6 (IL-6) and C-reactive protein (CRP) levels in colorectal adenoma and polyp patients. Vascular Pharmacology 2006; 44(5): 377-383.

64. Lakka HM, Lakka TA, Rankinen T et al. The TNF-α G-308A polymorphism is associated with C-reactive protein levels: the HERITAGE Family Study. Vascular Pharmacology 2006; 44(5): 377-383.

65. Nielsen FR, MøllerBek K, Rasmussen PE, Qvist I, Tobiassen M. CRP does not cross the placental barrier, and may therefore be useful in diagnosing infections in newborns. Biochem 2007; 40(5-6): 330-335.

66. Malek A, Bersinger NA, Di Santo S, Mueller MD, Sager R, Schneider H, et al. C-reactive protein production in term human placental tissue. Placenta 2006; 27(6-7): 619-625.
autoimmune diseases. J Korean Med Sci. 2011;26(9):1147-1151.

68. Kang YA, Kwon SY, Yoon HI, Lee JH, Lee CT. Role of C-reactive protein and procalcitonin in differentiation of tuberculosis from bacterial community acquired pneumonia. Korean J Intern Med. 2009;24(4):337-342.

69. Karouli S, Ouerdiane S, Serghini M, Jonni T, Kallel L, Fekih M, et al. Correlation between levels of C-reactive protein and clinical activity in Crohn’s disease. Dig Liver Dis 2007;39(11):1006-1010.

70. Hajati AK, Alstergren P, Näström K, Bratt J, Kopp S. Endogenous glutamate in association with inflammatory and hormonal factors modulates bone tissue resorption of the temporomandibular joint in patients with early rheumatoid arthritis. J Oral MaxillofacSurg 2009;67(9):1895-1903.

71. Shah T, Casas JP, Cooper JA, Tzoulaki I, Sofat R, McCormack V, et al. Critical appraisal of CRP measurement for the prediction of coronary heart disease events: new data and systematic review of 31 prospective cohorts. Int J Epidemiol 2009;38(1):217-231.

72. Sajadieh, Nielsen OW, Rasmussen V, Ole Hein H, Hansen JF. Increased ventricular ectopic activity in relation to C-reactive protein, and NT-pro-brain natriuretic peptide in subjects with no apparent heart disease. Pacing Clin Electrophysiol 2006;29(11):1188-1194.

73. Schell-indertSP, SchwaerzerR, Gphler A, Grandi N, GrabeInK, Stollenwerk B, et al. Prognostic value, clinical effectiveness and cost-effectiveness of high-sensitivity C-reactive protein as a marker in primary prevention of major cardiac events. 2009;5:1861-8863.

74. Badran HM, Einoamony MF, Khallil TS, Eldin MM. Age-related alteration of risk profile, inflammatory response, and angiographic findings in patients with acute coronary syndrome. Clin Med Cardiol 2009;18(3):15-28.

75. Williams ES, Shah SJ, Ali S, Na BY, Schiller NB, Whooley MA. C-reactive protein, diastolic dysfunction, and risk of heart failure in patients with coronary disease: Heart and Soul Study. Eur J Heart Fail 2008;10(1):63-69.

76. Nolan RP, Reid GJ, Seidelin PH, Lau HK. C-reactive protein modulates vagal heart rate control in patients with coronary artery disease. ClinSci (Lond) 2007;112(8):449-456.

77. Wilson PW, Pencina M, Jacques P, Selhub J, D’Agostino R Jr, O’Donnell CJ. C-reactive protein and reclassification of cardiovascular risk in the Framingham Heart Study. Circ Cardiovasc Qual Outcomes 2008;1(2):92-97.

78. Perry TE, Muehlischlegel JD, Liu KY, Fox AA, Collard CD, Body SC, Sherman SK; CABB Genomics Investigators. Preoperative C-reactive protein predicts long-term mortality and hospital length of stay after primary, nonemergent coronary artery bypass grafting. Anesthesiology 2010;112(3):607-613.

79. Miller RG, Costacou T, Orchard TJ. Lipoprotein-associated phospholipase A2, C-reactive protein, and coronary artery disease in individuals with type 1 diabetes and macroalbuminuria. Diab Vasc Dis Res 2010;7(1):47-55.

80. Nakou ES, Liberopoulos EN, Milionis HJ, Elisaf MS. The role of C-reactive protein in atherosclerotic cardiovascular disease: an overview. Curr Vasc Pharmacol 2010;6(4):258-270.

81. Burke AP, Tracy RP, Kolodziej F, Malcom GT, Zieske A, Kutys R, et al. Elevated C-reactive protein values and atherosclerosis in sudden coronary death: association with different pathologies. Circulation 2002;105(17):2019-2023.

82. Xu T, Ju Z, Tong W, Hu W, Liu Y, Zhao L, Zhang Y. Relationship of C-reactive protein with hypertension and interactions between increased C-reactive protein and other risk factors on hypertension in Mongolian people, China. Circ J 2008;72(8):1324-1328.

83. Magen E, Mishal J, Paskin J, Glick Z, Yosely C, Kidon M, et al. Resistant arterial hypertension is associated with higher blood levels of complement C3 and C-reactive protein. J Clin Hypertens 2008;10(9):677-683.

84. Iwashima Y, Horio T, Kamide K, Rakugi H, Ogihara T, Kawano Y. C-reactive protein, left ventricular mass index, and risk of cardiovascular disease in essential hypertension. Hypertens Res. 2007;30(12):1177-1185.

85. Tsiofus C, Stougiannos P, Kakavas A, Toutouza M, Mariliotis A, Vlasseross I, Stefanacidis C, Kalikazarios I. Relation of left ventricular concentric remodeling to levels of C-reactive protein and serum amyloid A in patients with essential hypertension. Am J Cardiol. 2005;96(2):252-256.

86. Cottone S, Milè G, Nardi E, Vadala A, Guameri M, Biriolotta C, Arsenia R, Palermo A, Riccobene R, Cerasola G. Relation of C-reactive protein to oxidative stress and to endothelial activation in essential hypertension. Am J Hypertens. 2006;19(3):313-318.

87. Lee YS, Ryu SY, Park J, Kang MG, Kim KS. [The association of high sensitivity C-reactive protein (hsCRP) with hypertension in some rural residents]. J Prev Med Public Health. 2005;38(3):325-329.

88. Kaplan RC, McGinn AP, Baird AE, Hendrix SL, Koopercberg C, Lynch J, et al. Inflammation and hemostasis for predicting stroke in postmenopausal women: the Women’s Heart Initiative Observational Study. J Stroke CerebrovascDis 2008;17(6):344-355.

89. Icdula TT, Brogger J, Naess H, Waje-Andreassen U, Thomassen L. Admission C-reactive protein after acute ischemic stroke is associated with stroke severity and mortality: the ‘Bergen stroke study’. BMC Neurol 2009;289-18.

90. Everett BM, Kurth T, Buring JE, Ridker PM. The relative strength of C-reactive protein and lipid levels as determinants of ischemic stroke compared with coronary heart disease in women. J Am Coll Cardiol 2006;48(11):2235-2242.

91. Elkind MS, Luna JM, Moon YP, Liu KM, Sptalinik SL, Paic MC, Sacco RL. High-sensitivity C-reactive protein predicts mortality but not stroke: the Northern Manhattan Study. Neurology 2009;73(16):1300-1307.

92. Elkind MS, Leon V, Moon YP, Paic MC, Sacco RL. High-sensitivity C-reactive protein and lipoprotein-associated phospholipase A2 stability before and after stroke and myocardial infarction. Stroke 2009;40(10):3233-3237.

93. Kosaku Komiya, Hiroshi Ishii, Shinji Teramoto, Osamu Takahashi, NobuokiEshima, Ou Yamaguchi, Nogiuki Ebi, Junji Murakami, Hidehiko Yamamoto and Jun-ichiKadota. Diagnostic utility of C-reactive Protein combined with brain natriuretic peptide in acute pulmonary edema: a cross sectional study. Respiratory Research 2011;12:83.

94. Urbanoiene D, Sakalauskas R, Sitkauskieni B. C-reactive protein levels in patients with chronic obstructive pulmonary disease and asthma. Medicina (Kaunas) 2008;44(11):833-840.

95. Garcia-Rio F, Miravillies M, Soriano JB, Muñoz L, Duran-Tauleria E, Sánchez G, Sobradillo V, Ancochea J; EPI-SCAN Steering Committee. Systemic inflammation in chronic obstructive pulmonary disease: a population-based study. Respir Res 2010;11:63.

96. Kwon YS, Chi SY, Shin HJ, Kim EY, Yoon BK, Han HJ, et al. Plasma C-reactive protein and endothelin-1 level in patients with chronic obstructive pulmonary disease and pulmonary hypertension. J Korean Med Sci 2010;25(10):1487-1491.

97. Pinto-Plata VM, Müllerova H, Toso JF, Feudjo-Tepie M, Soriano JB, Vessey JS, Celi BR. C-reactive protein in patients with COPD, control smokers and non-smokersThorax2006;61(1):23-28.

98. Pandolfi A. C-reactive protein: A potential new molecular link between inflammation, thrombosis and vascular cell proliferation. Cardiovascular Research 2005;34.
factor for left ventricular hypertrophy in patients with lupus nephritis. JBiomed Biotechnol 2010;37(4):26.

100. Simaney AM, Dowd JB, Pawelec G, Melzer D, Dutta A, Aiello AE. Seropositivity to cytomegalovirus, inflammation, all-cause and cardiovascular disease-related mortality in the United StatesPLoS One 2011;6(2):e16103.

101. Nash DT. Relationship of C-reactive protein, metabolic syndrome and diabetes mellitus: potential role of statins. J Natl Med Assoc2009;97(12):1600-1607.

102. Lewis TT, Aiello AE, PhD, Sue Leurgans, PhD, Jeremiah Kelly, MD, and Lisa L. Barnes, PhD. Self-reported Experiences of Everyday Discrimination are associated with Elevated C-Reactive Protein levels in older African-American Adults. Brain BehavImmun 2010; 24(3): 438-443.

103. Lee S, Choe J-W, Kim H-K and Sung J. High-Sensitivity C-Reactive Protein and Cancer. J Epidemiology 2011;21(3):161-168.

104. Crumley AB, McMillan DC, McKerman M, Going JJ, Shearer CJ, Stuart RC. An elevated C-reactive protein concentration, prior to surgery, predicts poor cancer-specific survival in patients undergoing resection for gastro-oesophageal cancer. Br J Cancer 2006;94(11):1568-1571.

105. Kruse AL, Luebbers HT, Grätz KW. C-reactive protein levels: a prognostic marker for patients with head and neck cancer? Head Neck Oncol 2010;2:21.

106. Shiu YC, Lin JK, Huang CJ, Jiang JK, Wang LW, Huang HC, et al. Is C-reactive protein a prognostic factor of colorectal cancer? Dis Colon Rectum. 2008;51(4):443-449.

107. Tsilidis KK, Branchini C, Guallar E, Helzlsouer KJ, Erlinger TP, Platz EA. C-reactive protein and colorectal cancer risk: a systematic review of prospective studies. Int J Cancer 2008;123(5):1133-1140.

108. Kwon KA, Kim SH, Oh SY, Lee S, Han JY, Kim KH, et al. Clinical significance of preoperative serum vascular endothelial growth factor, interleukin-6, and C-reactive protein level in colorectal cancer. BMC Cancer 2010;10:203.

109. Ortega-Deballon P, Radais F, Facy O, d’Athis P, Masson D, Crumley AB, McMillan DC, McKerman M, Going JJ, Shearer CJ, Stuart RC. An elevated C-reactive protein concentration, prior to surgery, predicts poor cancer-specific survival in patients undergoing resection for gastro-oesophageal cancer. Br J Cancer 2006;94(11):1568-1571.

110. Kruse AL, Luebbers HT, Grätz KW. C-reactive protein levels: a prognostic marker for patients with head and neck cancer? Head Neck Oncol 2010;2:21.

111. Sidoroff M, Karikoski R, Raivio T, Savilahti E, Kolho KL. High-sensitivity C-reactive protein in paediatric inflammatory bowel disease. World J Gastroenterol 2010;16(23):2901-2906.

112. Kao AH, Wasko MC, Krishnaswami S, Wagner J, Edmundowicz D, Shaw P, et al. C-reactive protein and coronary artery calcium in asymptomatic women with systemic lupus erythematosus or rheumatoid arthritis. Am J Cardiol. 2008 Sep 15;102(6):755-60.

113. Peters JH, Greasby T, Lane N, Woolf A. Correlations between plasma levels of a fibronectin isoform subpopulation and C-reactive protein in patients with systemic inflammatory disease. Biomarkers 2009;14(4):250-257.

114. Huffman FG, Gomez GP, Zarini GG. Metabolic syndrome and high-sensitivity C-reactive protein in Cubans. Ethn Dis 2009;19(2):115-120.

115. Ford ES, Ajani UA, Mokdad AH. National Health and Nutrition Examination. The metabolic syndrome and concentrations of C-reactive protein among U.S. youth. Diabetes Care2005;28(4):878-881.

116. Ridker PM, Buring JE, Cook NR, Rifai N. C-reactive protein, the metabolic syndrome, and risk of incident cardiovascular events: an 8-year follow-up of 14719 initially healthy American women. Circulation 2003;107(3):391-397.

117. Onuc N, Ozutemiz O, Yuce A, Akarca US, Gunes G, Gunes F, et al. Serum procollagen I and CRP levels in non-alcoholic fatty liver disease: a case control study. BMC Gastroenterology 2009;9:16.

118. Kravitz BA, Corrada MM, Kawas CH. Elevated C-reactive protein levels are associated with prevalent dementia in the oldest-old. Alzheimers Dement. 2009;5(4):318-323.

119. Roberts RO, Geda YE, Knopman DS, Boeve BF, Christianson TJ, Pankratz VS, et al. Association of C-reactive protein with mild cognitive impairment. Alzheimers Dement 2009;5(5):398-405.

120. Devaraj S, Siegel D, Schiffrin E, Smolen J, et al. Validation of the 28-joint Disease Activity Score (DAS28) and European League Against Rheumatism response criteria based on C-reactive protein against disease progression in patients with rheumatoid arthritis, and comparison with the DAS28 based on erythrocyte sedimentation rate. Ann Rheum Dis 2009;68(6):954-960.

121. Zimmerman O, Rogowski O, Aviram G, Mizrahi M, Zeltser D, Justo D, et al. C-reactive protein serum levels as an early predictor of outcome in patients with pandemic H1N1 influenza A virus infection. BMC Infect Dis. 2010;10:288.

122. Zhang J, She D, Feng D, Jia Y, Xie L. Dynamic changes of serum soluble triggering receptor expressed on myeloid cells-1 (sTREM-1) reflect sepsis severity and can predict prognosis: a prospective study. BMC Infect Dis 2011;11:53.

123. Poole CD, Conway P, Currie CJ. An evaluation of the association between C-reactive protein, the change in C-reactive protein over one year, and all-cause mortality in chronic immune-mediated inflammatory disease managed in UK general practice. Rheumatology (Oxford) 2009;48(1):78-82.

124. Nosdorff M, Karikoski R, Raivio T, Savilahti E, Kolho KL. High-sensitivity C-reactive protein in paediatric inflammatory bowel disease. World J Gastroenterol 2010;16(23):2901-2906.

125. Kao AH, Wasko MC, Krishnaswami S, Wagner J, Edmundowicz D, Shaw P, et al. C-reactive protein and coronary artery calcium in asymptomatic women with systemic lupus erythematosus or rheumatoid arthritis. Am J Cardiol. 2008 Sep 15;102(6):755-60.

126. Peters JH, Greasby T, Lane N, Woolf A. Correlations between plasma levels of a fibronectin isoform subpopulation and C-reactive protein in patients with systemic inflammatory disease. Biomarkers 2009;14(4):250-257.

127. Huffman FG, Gomez GP, Zarini GG. Metabolic syndrome and high-sensitivity C-reactive protein in Cubans. Ethn Dis 2009;19(2):115-120.

128. Ford ES, Ajani UA, Mokdad AH. National Health and Nutrition Examination. The metabolic syndrome and concentrations of C-reactive protein among U.S. youth. Diabetes Care 2005;28(4):878-881.

129. Ridker PM, Buring JE, Cook NR, Rifai N. C-reactive protein, the metabolic syndrome, and risk of incident cardiovascular events: an 8-year follow-up of 14,719 initially healthy American women. Circulation 2003;107(3):391-397.

130. Onuc N, Ozutemiz O, Yuce A, Akarca US, Gunes G, Gunes F, et al. Serum procollagen I and CRP levels in non-alcoholic fatty liver disease: a case control study. BMC Gastroenterology 2009;9:16.

131. Kravitz BA, Corrada MM, Kawas CH. Elevated C-reactive protein levels are associated with prevalent dementia in the oldest-old. Alzheimers Dement. 2009;5(4):318-323.

132. Roberts RO, Geda YE, Knopman DS, Boeve BF, Christianson TJ, Pankratz VS, et al. Association of C-reactive protein with mild cognitive impairment. Alzheimers Dement 2009;5(5):398-405.
133. Thorand B, Löwel H, Schneider A, Kolb H, Meisinger C, Fröhlich M, Koenig W. C-reactive protein as a predictor for incident diabetes mellitus among middle-aged men: results from the MONICA Augsburg cohort study, 1984-1998. Arch Intern Med 2003;163(1):93-99.

134. Lee HM, Lopez VA, Le TY, Wong ND. Association of C-reactive protein with reduced forced vital capacity in an nonsmoking U.S. population with metabolic syndrome and diabetes. Diabetes Care 2008;31:2000-2002.

135. Hu G, Jousilahti P, Tuomilehto J, Antikainen R, Sundvall J, Salomaa V. Association of serum C-reactive protein level with sex-specific type 2 diabetes. J Clin Endocrinol Metab 2009;94(6):2099-2105.

136. Kawamoto R, Tabara Y, Kohara K, Miki T, Kusunoki T, Takayama S, et al. High-sensitivity C-reactive protein and gamma-glutamyltransferase levels are synergistically associated with metabolic syndrome in community-dwelling persons. Cardiovasc Diabetol 2010;9:87.

137. Panaszek B, Liebhart E, Liebhart J, Pawłowicz R, Fal AM. Serum concentration of C-reactive protein is not a good marker of bronchial hyperresponsiveness. Arch Immunol Ther Exp (Warsz) 2007;55(5):341-345.

138. Olafsdottir IS, Gislon T, Thjodleifsson B, Olafsson I, Gislon D, Jögi R, et al. Serum C reactive protein levels are increased in non-allergic but not allergic asthma: a multicentre epidemiological study. Thorax 2005;60(6):451-454.

139. Melbye H, Hvidsten D, Holm A, Nordbo SA, Brox J. The course of C-reactive protein response in untreated upper respiratory tract infection. Br J Gen Pract 2004; 54(506): 653–658.

140. Soriano S, González L, Martín-Malo A, Rodríguez M, Aljama P. C-reactive protein and low albumin are predictors of morbidity and cardiovascular events in chronic kidney disease (CKD) 3-5 patients. Clin Nephrol 2007;67(6):352-357.

141. Abraham G, Sundaram V, Sundaram V, Mathew M, Leslie N, Sathish V. C-Reactive protein, a valuable predictive marker in chronic kidney disease. Saudi J Kidney Dis Transpl 2009;20(5):811-815.

142. Menon V, Wang X, Greene T, Beck GJ, Kusek JW, Marcovina SM, et al. Relationship between C-reactive protein, albumin, and cardiovascular disease in patients with chronic kidney disease. Am J Kidney Dis 2003;42(1):44-52.

143. Menon V, Greene T, Wang X, Pereira AA, Marcovina SM, Beck GJ, et al. C-reactive protein and albumin as predictors of all-cause and cardiovascular mortality in chronic kidney disease. Kidney Int 2005;68(2):766-772.

144. Golbasi Z, Ucar O, Keles T, Sahin A, Caglic K, Camsari A, Diker E, Aydogdu S. Increased levels of high sensitive C-reactive protein in patients with chronic rheumatic valve disease: evidence of ongoing inflammation. Eur J Heart Failure 2002;4:593-595.

145. Locascio JJ, Fukimoto H, Yap L, Bottiglieri T, Growdon JH, Hyman BT, et al. Plasma amyloid beta-protein and C-reactive protein in relation to the rate of progression of Alzheimer disease. Arch Neurol 2008;65(6):776-785.