Review: Biology and Relevance of C-Reactive Protein in Cardiovascular and Renal Disease

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Abstract. C-reactive protein (CRP) is a member of the pentraxin family of proteins, which are characterised by a cyclic pentameric structure and radial symmetry. The five identical 24-kDa protomers consist of 206 amino acids, and are noncovalently linked. CRP binds to a range of substances such as phosphocholine, fibronectin, chromatin, histones, and ribonucleoprotein in a calcium-dependent manner. It is a ligand for specific receptors on phagocytic leukocytes, mediates activation reactions on monocytes and macrophages, and activates complement. Plasma CRP is the classical acute-phase protein, increasing 1,000-fold in response to infection, ischemia, trauma, burns, and inflammatory conditions. A growing number of studies suggest that CRP is an independent risk factor for atherosclerotic vascular disease. Plasma CRP concentrations in the highest quartile are associated, depending on the subject group, with 1.5- to 7-fold increases in relative risk. In the high-risk endstage renal failure population, a raised CRP is associated with up to 5.5-fold increased relative risk of CVD and 4.6-fold increased relative risk of death. This review examines the relationships between CRP, cardiovascular disease, and mortality, with special reference to renal disease.

Keywords: Acute-phase reactants, C-reactive protein, cardiovascular disease, end-stage renal failure, pentraxins

Introduction

C-reactive protein (CRP) is a member of the highly conserved family of proteins, termed pentraxins, that have been found in all vertebrate species studied [1]. CRP is the major acute-phase protein in man, responding to inflammatory stimuli with increased hepatic synthesis and a 1,000-fold increase in plasma concentration [2,3]. It binds to microbial polysaccharides and phosphatidylcholine in a calcium-dependent manner, promotes the activity of phagocytic cells [3,4], and activates the classical complement pathway at C1q [5].

It has only recently become clear that inflammation is an important process in the pathogenesis of atherosclerosis [6]. A growing number of studies suggest that an elevation of CRP concentration is associated with an increased risk for cardiovascular disease (CVD) [6-8]. Associations have been reported in apparently healthy people, the elderly, and in various high risk groups [8]. Subjects in end-stage renal failure (ESRF) are a group with a particularly high risk of atherosclerosis, partly due to factors such as deranged lipoprotein metabolism, diabetes, hypertension, hyperhomocysteinemia, and recurrent inflammatory insults [9,10]. CRP is frequently raised in the serum of those with ESRF [11], and this raises the question of the role of inflammatory processes, flagged by elevated CRP, in the pathogenesis of the increased risk of CVD and death in this population. The present review updates the clinical biochemistry of CRP and concentrates on the association between CRP, CVD, and mortality, with particular reference to subjects with renal disease. Readers are referred to earlier reviews for further information [1-3,12-16].
Structure of CRP

CRP belongs to the pentraxin family of proteins with sequence homologies to serum amyloid P component (SAP), a short pentraxin, and the long pentraxin TSG-14/PTX3, derived from endothelial cells [1]. These proteins are characterised by a cyclic pentameric structure with radial symmetry, and calcium-dependent ligand binding [1,17,18]. Each of the five identical 24-kDa subunits of CRP consist of 206 amino acids; the subunits are noncovalently linked to each other. Human, rabbit, horse, and cow CRPs are not glycosylated, but CRPs from other species are [16]. In the rat, for example, a single oligosaccharide chain is attached to the Asn-128 residue of each monomer [19].

Synthesis of CRP

CRP is normally synthesised by hepatocytes at relatively low rates and retained in the endoplasmic reticulum (ER) via interaction with two carboxylesterases (gp60a and gp60b) [20]. The latter are retained in the ER by their COOH-terminal retention signals, HIEL and HTEL [20]. During the acute phase response, there is an increase in CRP synthesis and a decrease in CRP binding affinity for gp60b, resulting in the release of relatively large amounts of CRP into the circulation and a fall of CRP in the ER [20]. In addition, CRP levels increase in physiological states like the menstrual cycle, where it correlates with progesterone levels [21]. As its fractional catabolic rate is independent of plasma CRP level, the major determinant of plasma CRP concentration is its rate of synthesis [22].

CRP may also be synthesized extrahepatically. A subset of stimulated lymphocytes (but not monocytes) produce a surface peptide that is recognised by anti-CRP antibodies [23]. Human peripheral blood mononuclear cells (PBMC) have been shown to express a transcript of the CRP gene. Expression of CRP by PBMC at sites of inflammation or malignancy suggests that CRP may mediate local inflammation and network the inflammatory and immune responses [24].

Distribution of CRP

Studies with iodinated CRP show that the plasma half-life of CRP in man is about 19 hr, which is shorter than that of most plasma proteins [22]. About 70% of the protein is estimated to be intravascular. Plasma clearance closely approximates a monoeponential function, suggesting a single pool distribution model. Its distribution is unaffected by the presence of inflammatory disease [22]. Furthermore, imaging studies with $^{123}$I-labelled CRP in subjects with diverse focal pathologies show no significant localisation of tracer [22]. These researchers therefore suggest that the functions of CRP are likely to occur predominantly in the fluid phase rather than the tissue phase of deposition at sites of inflammation or tissue injury [22]. This view does not exclude a role for CRP localised within tissues at inflammatory sites. CRP is present in human atherosclerotic lesions, including within CD68+ foam cells [1], and binds to nuclear material such as histones and ribonucleoprotein [4,17,25]. In mice, parenteral CRP localises selectively in the bone marrow [26]. CRP may therefore have significant functions within tissues as well as those of its fluid phase. However, the biochemically active form of CRP may differ between the two phases [27].

Excretion of CRP

Studies with iodinated CRP in mice show that CRP appears to be excreted in the urine [26]. The levels in urine, however, are low. In patients with secondary amyloidosis and proteinuria, only negligible amounts of CRP are detected in 24-hr urine specimens [28]. Presumably, the bulk of the filtered protein is reabsorbed by the tubules. Whether filtered CRP has effects on tubular cells and on the promotion (or inhibition) of tubulointerstitial injury is, to our knowledge, unknown.

Cell Biology of CRP

A characteristic of CRP is that the protein binds phosphoethanolamine and phosphocholine [29,30], thus recognising foreign pathogens like the pneumococcus organisms (by binding to phosphocholine) as well as disrupted cell membranes. Under certain conditions, CRP also binds to SAP [31]. The three-dimensional structure suggests that phosphocholine binding involves a hydrophobic pocket centered on the Phe-66 residue [18] and involving...
Lys-57, Arg-58, and Trp-67 [32]. Glu-81 is positioned nearby and can interact with the choline group [18].

CRP binds to specific receptors on macrophages, monocytes, and neutrophils. A peptide of residues 27-38, termed the cell-binding peptide (CB-Pep), mediates CRP attachment to cells in vitro [33,34]. It has been suggested that CB-Pep is generated from the degradation of CRP at sites of tissue injury or inflammation, thereby facilitating CRP binding to PMN [35]. Competitive binding studies with truncated peptides suggest that the minimum length recognised by the CRP receptor consists of residues 31-36 (KAFTVC) [35], although other workers report the functionally active sequence is residues 33-37 (FTVCL) [33]. The sequence is present in each of the five subunits of CRP and is postulated to serve as a unique recognition motif for inflammatory leukocytes [33,34].

CRP activates the classical pathway of complement [5]. Since complement has been implicated in proteinuria-associated tubulointerstitial injury [36,37], CRP may be involved in inflammatory responses in the kidney, and possibly progression of renal damage. The optimum pH for complement activation is 6.3, which is within the range observed at inflammatory loci [38]. Complement components C1 and C4 are initially consumed, followed by C2 and C3, with only minor consumption of C5 [38]. These are the early stages of the activation of the complement cascade. CRP binds preferentially to the collagen-like region (CLR) of the A chain of C1q via two cationic sites within residues 14-26 and 76-92 [39].

CRP may also be involved in the modulation of platelet activation during an acute inflammatory response. CRP inhibits platelet-activating factor (PAF)-induced aggregation of human platelets in a time- and dose-dependent manner [40]. It appears to act either by preventing PAF binding to platelets, or possibly by displacing previously bound PAF from platelets [40].

Like the related compound SAP, CRP interacts with nuclear components including chromatin and small nuclear ribonucleoproteins in intact cells [17,25,41,42]. Both CRP and SAP possess nuclear transport signals that facilitate their entry into the nucleus [17]. CRP binding to small nuclear ribonucleoproteins depends on calcium ions, and is inhibited by phosphocholine. It is postulated that one of the chief functions of CRP and SAP is binding to nuclear antigens released from apoptotic or necrotic cells, thereby reducing their tissue deposition and limiting autoimmune reactivity [17]. Failure of immune surveillance mechanisms like these have the potential to lead to autoimmune diseases including glomerulonephritis.

CRP binds to several other endogenous ligands, including the glycoproteins laminin, an adhesive molecule specific for basal lamina, and fibronectin, the principal adhesive molecule in connective tissue [13,43]. CRP also binds to low-density lipoprotein (LDL) and very low-density lipoprotein (VLDL) [44]. The latter interactions, however, are weak, and CRP-lipoprotein complexes are not normally observed in the circulation [13,44].

The biological properties of CRP are summarized in Table 1.

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Table 1. Biological properties of CRP

<table>
<thead>
<tr>
<th>Property</th>
<th>Description</th>
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<tbody>
<tr>
<td>Structure</td>
<td>Cyclic pentamer with radial symmetry, five identical protomers of 206 amino acids, molecular weight of 23,048, non-covalently linked [1,12,17,18]. Non-glycosylated in humans [16]. Ligand-binding site contains 2 ligated Ca(^{2+}) ions [18].</td>
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<tr>
<td>Synthesis</td>
<td>Primarily hepatic, possibly peripheral blood mononuclear cells [20,23,24]. Inducible by cytokines [46,68].</td>
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<tr>
<td>Ligand-binding</td>
<td>Phosphocholine, phosphoethanolamine [29,30], chromatin, histones, small nuclear ribonucleoprotein [17,25,42], cell-binding peptide (CB-Pep) [33,34], laminin &amp; fibronectin [43], LDL &amp; VLDL (weakly) [44].</td>
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<tr>
<td>Physiological functions</td>
<td>Activates complement [5], modulates platelet activation [40], modifies immune effector cell behavior [12,13], binds nuclear antigens released from apoptotic or necrotic cells [17,41].</td>
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<td>Pathophysiology</td>
<td>Acute-phase reactant [2], inflammatory marker [3], possible risk factor for CVD [8] and mortality [9,64,76], present in atherosclerotic plaque [69,70].</td>
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Molecular Biology of CRP

The pentraxin genes (which include CRP, SAP, and a CRP pseudogene) have been assigned to the q21 to 25 region of human chromosome 1. This region contains genes which encode proteins with immune- and inflammation-associated functions [45]. Neighbouring genes include the FCER1A gene, which encodes the α-subunit of the IgE high-affinity Fc receptor, the IFI-16 gene, a gene induced by interferon, the histone genes H3F2 and H4F2, and the gene for erythroid α-spectrin (SPTA1) [45]. Studies in transgenic mice suggest that the human CRP gene (hCRP) is induced by lipopolysaccharide and wounding, and depends indirectly on interleukin-6 (IL-6) [46]. The cytokines IL-1β, oncostatin M, and leukemia inhibitory factor also induce hCRP [46].

In mouse liver, some acute phase proteins are induced by hyperthermia—for example, CRP and the α1-acid glycoproteins, AGP-1 and AGP-2. Others are not—for example, serum amyloid A and α1-antitrypsin. On the other hand, albumin, a negative acute phase protein, is upregulated, not downregulated by hyperthermia [47]. It is hypothesised that cis-acting heat shock elements (HSE), located in the promoter regions of the albumin and CRP genes, regulate activation of these genes during hyperthermia. There are also reports linking up-regulation of heat shock proteins (HSP) with activity of renal disease [48] and with dialysis treatment [49]. HSP are best known as cytoprotective agents. Their induction can be seen as a response to the stress of the underlying renal disease, as well as the cardiovascular comorbidity and the inflammatory stress of HD.

Dialysis with bioincompatible membranes appears to upregulate CRP. The evidence is, however, indirect and is based on the observations of, firstly, transient increases in complement during the early stages of dialysis with bioincompatible membranes [50,51], and secondly, the correlation between raised CRP levels and increasing time on HD [11]. However, serum CRP levels do not change significantly during a dialysis treatment using either bioincompatible Cuprophan membranes or biocompatible cellulose acetate and polymethylmethacrylate membranes [52]. Moreover, cytokine levels do not change during a dialysis treatment [53-55]. Thus, a clinically relevant relationship between haemodialysis, hyperthermia, and increases in CRP appears unlikely.

CRP and Cardiovascular Disease

While atherosclerosis is clearly multifactorial in origin, evidence suggests that chronic inflammation is an important component in the pathogenesis. This is supported by recent research suggesting that CRP, the "prototype" acute phase reactant, is an independent risk factor for CVD. Since atherosclerosis remains the major cause of mortality in ESRF patients [56], these studies are of particular significance and will be summarised in some detail (Table 2).

In apparently healthy men participating in the Physician's Health Study and followed for five years, median CRP levels at entry were significantly higher among those who subsequently developed symptomatic peripheral artery disease (PAD) [57]. Relative risk for PAD increased from lowest to highest tertile of concentration (P_trend = 0.02), and was independent of body mass index, hypercholesterolemia, hypertension, diabetes, and family history of premature atherosclerosis. CRP was a risk factor additional to total cholesterol and HDL cholesterol in predicting future MI [58]. Aspirin use was associated with a reduction in risk of myocardial infarction (MI), and this appeared to be directly related to the level of CRP [59]. Similarly, in the MONICA-Augsburg study, randomly selected middle-aged men followed for up to eight years had a 2.6-fold increase in CVD risk if CRP concentrations were in the highest quintile [60]. CRP appears to be an even stronger risk factor for CVD in women. In an apparently healthy cohort, those with the highest levels of CRP had a 5-fold increase in risk of any cardiovascular event and a 7-fold increase in risk of MI or stroke over the next three years [61]. CRP was independent of and additive to other risk factors in predictive risk models. CRP is also associated with increased risk of CVD in the elderly [62]. The associations with MI were particularly strong. Odds ratios were 4.5 in women and 1.75 in men for the highest quartile of CRP, versus the lower three quartiles [62]. Interleukin-6 (IL-6) may be another additive risk factor for mortality in populations with high CRP concentrations [63].
Table 2. CRP as a risk factor for cardiovascular disease and mortality: summary of prospective studies.

<table>
<thead>
<tr>
<th>Authors/study</th>
<th>Study description</th>
<th>Duration of follow-up</th>
<th>Principal findings (CRP)</th>
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<tbody>
<tr>
<td>Danesh et al, 1998 [8]</td>
<td>Meta-analysis of 7 prospective studies</td>
<td>Variable</td>
<td>1.7-fold increase in relative risk of combined CVD endpoints (highest vs lowest tertile at baseline)</td>
</tr>
<tr>
<td>Physician's Health Study [59]</td>
<td>Randomised, controlled trial (RCT) 8 yr of apparently healthy middle-aged men of aspirin vs placebo</td>
<td>8 yr</td>
<td>2.9-fold increase in risk of MI and 1.9-fold for ischemic stroke (highest vs lowest quartile). Aspirin use reduced risk of MI by 55.7% for subjects in highest quartile for CRP concentration.</td>
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<tr>
<td>MONICA-Augsburg Cohort Study [60]</td>
<td>Randomised prospective study of initially healthy men aged 45-64 yr (n=936)</td>
<td>8 yr</td>
<td>2.6-fold increase in relative risk of a future coronary event (highest vs lowest quintile). Risk independent of age, smoking, body mass index, diabetes</td>
</tr>
<tr>
<td>Physician's Health Study [57]</td>
<td>Prospective, nested, case-control study of apparently healthy middle-aged men; 144 cases, 144 controls</td>
<td>5 yr</td>
<td>2.1-fold increase in relative risk for symptomatic peripheral artery disease (highest vs lowest tertile of concentration)</td>
</tr>
<tr>
<td>Cardiovascular Health Study &amp; Rural Health Promotion [62]</td>
<td>Prospective, nested, case-control study of the elderly; 146 CVD cases, 146 controls</td>
<td>2.4 yr</td>
<td>Odds ratio for MI 1.75 in men, 4.5 in women (highest vs lower three quartiles)</td>
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<tr>
<td>Kuller et al, 1996 MRFIT Research Group [64]</td>
<td>Nested, case-control study of healthy but high-risk men, aged 35-57; 246 cases, 491 controls</td>
<td>17 yr (deaths), 7 yr (MI)</td>
<td>4.3-fold increase in risk of CHD mortality in smokers (highest vs lowest quartile of CRP conc). No increase in risk of non-fatal MI (odds ratio 1.0)</td>
</tr>
<tr>
<td>Physician's Health Study [58]</td>
<td>Prospective study of apparently healthy middle-aged men; 246 cases, 372 age- &amp; smoking-matched controls</td>
<td>≤ 9 yr</td>
<td>5-fold increase in relative risk of first MI if both CRP and cholesterol in upper quartile at baseline, relative risk of 1.5 if cholesterol not in upper quartile</td>
</tr>
<tr>
<td>Ridker et al, 1998 [61]</td>
<td>Prospective, case-control study of apparently healthy women; 122 cardiovascular cases, 244 controls matched for age and smoking history</td>
<td>3 yr</td>
<td>5-fold increase in risk of cardiovascular events; 7-fold increase in risk of MI/stroke (highest vs lowest quartile)</td>
</tr>
<tr>
<td>Harris et al, 1999 [63]</td>
<td>Population-based, prospective study of non-disabled elderly; 176 deaths, 499 survivors (n=675)</td>
<td>4.6 yr</td>
<td>Relative risk of 1.6 for death (highest vs lowest quartiles of CRP concentration). Risk increased to 2.6 for subjects with IL-6 values in highest quartile</td>
</tr>
<tr>
<td>ECAT Angina Pectoris Study [65]</td>
<td>Prospective study of stable and unstable angina patients; 1797 men, 324 women</td>
<td>2 yr</td>
<td>2-fold increase in relative risk of coronary events (highest vs lower four quintiles)</td>
</tr>
<tr>
<td>Pietila et al, 1996 [67]</td>
<td>Prospective study of 188 consecutive patients undergoing thrombolytic treatment for MI (154 men, 34 women aged 25-88 yr)</td>
<td>2 yr</td>
<td>CRP concentration peaked 2-4 days post-MI. Death within 6 mo was associated with significantly higher peak CRP values. 2 yr survival was associated with lowest peak CRP values</td>
</tr>
<tr>
<td>Zimmermann et al, 1999 [9]</td>
<td>Prospective study of stable, white HD patients, 130 women, 150 men, aged 20-88 yr</td>
<td>2 yr</td>
<td>5.5-fold increase in risk of cardiovascular mortality and 4.6-fold increase for all-cause mortality for baseline CRP in upper quartile</td>
</tr>
<tr>
<td>Iseki et al, 1999 [76]</td>
<td>Prospective study of chronic dialysis patients, 95 men, 68 women</td>
<td>5 yr</td>
<td>3.5-fold increase in relative risk of death if CRP at baseline was above 9.9 mg/L</td>
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</table>
CRP is also a cardiovascular risk factor in groups identified as high-risk. The relative risk of coronary heart disease deaths over 17 years was 4.3-fold greater among smokers in the MRFIT trial whose CRP concentration was in the highest compared to the lowest quartile [64]. The association persisted after adjustment for lung function, blood thiocyanate levels, and white blood cell count [64]. The relative risk of a coronary event was similarly 2.0-fold higher among a cohort with angina, both stable and unstable, followed for two years and whose CRP concentration was in the highest compared with the lowest four quintiles (European Concerted Action on Thrombosis and Disabilities (ECAT) Angina Pectoris Study) [65]. Only troponin T and CRP were independently associated with MI in subjects with unstable angina pectoris [66]. Troponin T had higher specificity than CRP (92% vs 54%), but CRP had higher sensitivity (87% vs 47%) [66]. High serum CRP concentrations also predicted mortality for up to six months after MI in subjects treated with thrombolytic drugs [67]. In contrast, the heights of concentrations of serum creatine kinase or its MB isoenzyme were not associated with increased mortality. In a meta-analysis of seven prospective studies involving a total of 1053 cases, the combined risk ratio for CHD was 1.7-fold higher in those in the highest tertile of CRP compared to the lowest [8].

**Mechanisms.** While an association between CRP and CVD is now recognised, the mechanisms involved are unclear. Cytokines are possible mediators. CRP synthesis by the liver is regulated by cytokines, principally tumour necrosis factor α (TNF-α) and IL-6, both of which have intense proinflammatory, growth-promoting, and procoagulant effects [68]. Serum concentrations of TNF-α and IL-6 appear to relate to cardiovascular risk factors in a broadly similar way to CRP [68]. It is, however, difficult to separate cause and effect, as raised levels of cytokines may also be a consequence of inflammation in the arterial wall. Their role may therefore be to amplify rather than to initiate increased synthesis of CRP.

CRP has been shown by immunohistochemical staining with both polyclonal and monoclonal anti-human CRP antibodies to be present in necrotic human atherosclerotic lesions [69,70], but not in non-necrotic arteries [70]. CRP is present in intimas that are thickened and in early plaques located just beneath the endothelium [70]. It localises within CD68+ foam cells, suggesting an uptake of CRP-lipid complexes by macrophages. Intensity of immunoreactivity correlates positively with relative intimal thickness and negatively with relative lumen size. It is therefore postulated that the thickening of the intima and narrowing of the lumen are associated with an inflammatory process in arterial vascular tissue [70].

**Inflammation and CRP in Renal Disease**

Atherosclerotic CVD is the major cause of morbidity and mortality in subjects with advanced renal insufficiency, but the relationship between CRP and CVD has only recently been studied in this high-risk group. Advanced renal insufficiency is characterised by profound metabolic changes including, but not limited to, uremia, acid-base disturbances, dyslipidemia, and anemia. Activation of inflammatory markers is a feature, but their role in the pathogenesis of uremia and comorbid states is not well elucidated [71].

**Predialysis.** Predialysis subjects have an increased mean carotid intima to media area and a higher prevalence of carotid plaques, surrogate markers of cerebrovascular disease, compared to healthy controls [10]. The malnourished in this cohort, identified by subjective global assessment, had higher CRP levels, increased intima to media areas, and a higher prevalence of carotid plaques compared to “well-nourished” patients [10]. Chronic inflammation may cause muscle wasting, weight loss, and cachexia [72], which are also clinical signs of undernutrition. Discrimination between undernutrition and chronic inflammation may be difficult [72], but coexistence of the two is linked to increased risk of death [72-74]. CRP may also identify ESRF subjects at greater risk of hospitalisation [75].

**Dialysis.** The hypothesis of an inflammatory state during hemodialysis (HD) is supported by a correlation between raised CRP concentrations and time on treatment [11]. CRP concentrations in the upper quartile in 280 HD subjects were associated with a 4.6-fold increase in relative risk of all-cause mortality, and a 5.5-fold increase in risk of cardiovascular mortality over two years [9]. The relative risk factors
were 2.9 and 2.65-fold, respectively, for serum amyloid A [9]. A Japanese study of chronic dialysis subjects showed a 3.5-fold increase in the relative risk of death over five years if CRP at baseline was above the normal range (up to 9.9 mg/L). Mortality risk was independent of serum albumin concentrations [76]. However, the correlation is not evident over shorter follow-up times. CRP did not predict death in a cohort study of over 1000 nonhospitalised HD subjects followed for six months [74]. The association between CRP and relative risk of dying may be weaker in the PD population, where a 1.2-fold increase in mortality over two years has been reported [77]. The reason for the different findings in the PD population is not clear, but is likely to involve patient selection, dialysis modality, comorbidities, and length of followup. Studies are required to clarify the association of inflammation and mortality risk in ESRF populations.

Inflammatory responses may be related to bioincompatible dialysis membranes or exposure to residual chemicals in tubing and solutions, or comorbidities (e.g. occult or overt infection). CRP is commonly raised among malnourished [78] and elderly [79] dialysis subjects. It correlates with lipoprotein (a), an independent risk factor for CVD [78], and low serum albumin [80], a negative inflammatory marker and a marker of visceral protein nutrition.

The coexistence of an inflammatory state with ESRF may cause the relative erythropoietin (EPO) resistance observed in some subjects. ESRF is accompanied by decreased EPO production by the renal cortex, with subsequent development of anemia. While EPO administration reverses impaired erythropoiesis in most subjects, some have a blunted response [81]. Hemodialysis subjects in the latter group tend to have higher CRP concentrations (20 mg/L or greater) [82]. Levels of fibrinogen, a weak positive acute phase reactant, are elevated and albumin, the best predictor of EPO resistance in well-dialysed, iron-replete subjects, depressed [81,83]. Hyperparathyroidism and aluminum toxicity were not related to EPO resistance in either PD or HD patients [81] in these studies. Abnormalities in the iron profile, such as low transferrin and high ferritin, were attributed to inflammation rather than true iron deficiency [81].

**CRP and renal transplantation.** CRP does not predict renal allograft rejection, although other inflammatory markers like serum amyloid A protein do [84]. CRP does, however, appear to discriminate between infection and rejection [84-86]. Methods to optimise the discriminatory power of CRP include using serum to urinary CRP ratios [85,87], or including serum α2-macroglobulin, an acute phase reactant, and urinary granulocyte myeloperoxidase in the assessment [88].

**CRP and infection.** CRP continues to be a useful marker of the severity of urinary tract infections in children, despite false negative results [89], and of patient response to therapy. It parallels the ESR [90]. However, CRP is not recommended to discriminate between bacterial and viral diseases in children, in the differential diagnosis of acute appendicitis, or for the localisation of urinary tract infections [90].

**Albumin and renal insufficiency.** CRP was the strongest correlate of low serum albumin among a panel of parameters in multiple linear regression models in both HD subjects [80] and PD subjects [91]. The correlates were independent of nutritional status [78,80], supporting the hypothesis that albumin is a marker of an inflammatory pathogenesis. Serum albumin falls during inflammation because of reduced hepatic synthesis [80]. As mentioned above, low serum albumin is a stronger predictor of relative erythropoietin resistance than CRP in well-dialysed, iron-replete subjects [81]. Importantly, hypoalbuminemia is a predictor of death in HD subjects [80,92,93].

**Cytokines, inflammation, and renal insufficiency.** The observation that cytokine activity rises in parallel with renal insufficiency supports a hypothesis that they may mediate the pathogenesis of inflammation in populations with renal disease [94,95], as well as in other populations. Cytokines IL-1β, IL-6, IL-8, and TNFα have been implicated in ESRF subjects [94-97]. However a relationship of cytokines with inflammatory markers has not been firmly established in the renal insufficiency population.

**Concluding Remarks**

CRP is widely used as an inflammatory marker, but its routine use in the assessment of renal patients is problematic. End-stage renal failure is characterised by deranged metabolism as well as significant
comorbidities. Clearly, infection and inflammatory responses related to dialysis complicate the use of CRP as a monitoring index for other inflammatory states like atherosclerosis. However, most studies of the ESRF population suggest that CRP is an independent risk factor for CVD and mortality, as in other population groups. The high rate of CVD in ESRF has not been fully explained, and the inflammatory response may well assume greater importance in this patient group than has hitherto been noted in other high-risk groups. The relationship of CRP to CVD risk in these patients deserves further study.

Acknowledgments

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