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PERSPECTIVES IN RENAL MEDICINE

End-stage renal disease, atherosclerosis, and cardiovascular mortality: Is C-reactive protein the missing link?

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End-stage renal disease, atherosclerosis, and cardiovascular mortality: Is C-reactive protein the missing link? In uremic patients, the morbidity and mortality of cardiovascular disease are substantially higher than in the general population. This has led to the formulation of an "accelerated atherogenesis" hypothesis in uremic patients and has been commonly linked with the metabolic alterations associated with uremia. Advancement in the understanding of the pathogenesis of atherosclerotic vascular disease now suggests a central contribution of inflammation to atherogenesis, with involvement of a number of key mediators and markers of the inflammatory process. Recent epidemiological data have documented associations between C-reactive protein (CRP), the prototypical acute phase response protein, and cardiovascular disease in general population. Given the lipoprotein binding and complement activation functions of CRP and its localization in atherosclerotic vessels, there is a strong likelihood that CRP may be involved in the atherosclerotic process. The uremic state is associated with an altered immune response, which is associated with elevated proinflammatory cytokine levels. CRP concentrations are increased in a significant proportion of end-stage renal disease patients and have been associated with certain clinical outcome measures, including all-cause and cardiovascular mortality. This review outlines the evidence linking CRP with atherosclerosis and proposes that elevated CRP concentrations may be involved in the initiation and progression of accelerated atherosclerosis in uremia.

"*In our retrospective study, it is not possible to provide evidence of the cause of the accelerated atherosclerosis. The possible role of renal failure as an etiologic factor per se cannot be neglected.*" A. LINDNER ET AL, 1974 [1]

"*Atherosclerosis is an inflammatory disease . . . the process of atherogenesis has been considered by many to consist largely of the accumulation of lipids within the artery wall; however, it is much more than that.*" RUSSELL ROSS, 1999 [2]

Key words: uremia, dialysis, immune response, inflammatory disease, fatty streak lesion, fibrous plaque, vascular disease, acute phase response.

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Several studies from the early 1970s showed that the prevalence of cardiovascular diseases was significantly higher in uremic patients on maintenance hemodialysis (HD) compared with other populations of a similar age [1, 3, 4]. This led to the hypothesis of an "accelerated atherogenesis" in patients on dialysis [1]. The hypothesis still remains a matter of controversy, but the high mortality rate caused by cardiovascular complications remains despite the advances achieved in dialysis technology during last two decades. The cardiovascular mortality rate in dialysis patients is approximately 30 times the risk in the general population and remains 10 to 20 times higher even after stratification for age, gender, and presence of diabetes [5].

Undoubtedly, end-stage renal disease (ESRD) is associated with several traditional (hypertension, hyperlipidemia, diabetes mellitus) and uremia-related risk factors (hemodynamic overload, anemia, hyperhomocysteinemia, and increased oxidative stress) for atherogenesis [6]. The major focus of interest thus far has been devoted to finding a link between the metabolic alterations of chronic uremia and the development of atherosclerosis. However, over the last several years, the idea that inflammation plays a key role in atherosclerosis has received considerable attention. Atherosclerosis is not a single disease entity, but a process consisting of the responses to numerous insults to the endothelium and smooth muscle cells of the arterial wall. This "response-to-injury" hypothesis is formulated by numerous observations in humans and animals, and the whole process from the earliest recognizable lesion (fatty streak) to advanced lesions of atherosclerosis (fibrous plaques) is tightly linked with an inflammatory response (Fig. 1) [reviewed in 2].

In view of the persuasive evidence implicating a key role to inflammation in atherosclerosis, several circulating markers of inflammation have been examined as potential tools for predicting the presence of vascular disease or the risk of vascular events [7]. Of the variety of circulating markers, C-reactive protein (CRP), the major acute phase response (APR) protein, has been

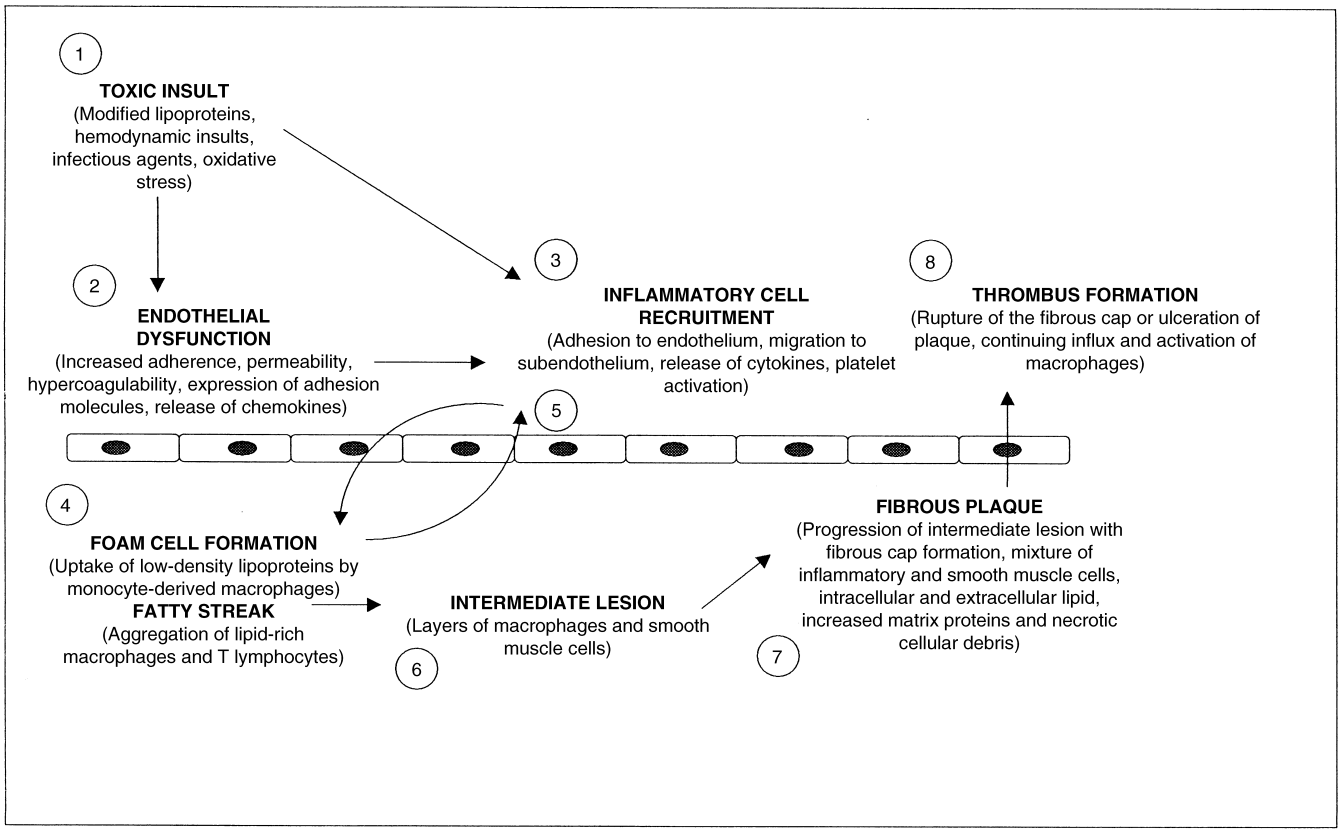

Fig. 1. Development of atherosclerotic lesions according to "response-to-injury" hypothesis [2]. The earliest changes that precede the formation of atherosclerosis take place in the endothelium (endothelial dysfunction), which is the result of exposure to various toxic insults. The endothelial cells increase expression of adhesion molecules and secrete various chemokines and growth factors. The increased adherence of monocyte/macrophages and T-cells precede their subendothelial migration. Subendothelial macrophages become large foam cells after lipid accumulation. The fatty streak can then progress to an intermediate lesion and ultimately to a fibrous plaque as a result of continued inflammation. The fibrous plaques increase in size and, by projecting into the lumen, may impede the blood flow and incite further thrombogenic stimuli.

the best studied, with the most consistent relationship to future risk for cardiovascular events in different clinical settings in general population [reviewed in 8, 9]. Accumulating data from prospective cohort studies in ESRD patients have also demonstrated an association between elevated CRP levels and all-cause and cardiovascular mortality [10, 11]. In this review, we summarize the currently available evidence regarding CRP, atherosclerosis, and cardiovascular disease in both the general population and uremic patients. We also consider the possible pathogenetic importance of CRP in atherosclerotic vascular disease. Elucidation of the role of CRP in the context of ESRD can help develop further insights for the hypothesis of "accelerated atherogenesis in uremia" and potential starting points for preventive measures.

CRP, ATHEROSCLEROSIS, AND CARDIOVASCULAR DISEASE

C-reactive protein is the prototypical APR protein produced by the liver under the control of various proinflammatory cytokines, namely interleukin-6 (IL-6), IL-1, and tumor necrosis factor-α (TNF-α). Its uniqueness is due to rapid (within 6 hours) and dramatic increases (up to 1000-fold) in circulating concentrations after a cytokine-mediated response to most forms of tissue injury, infection, and inflammation [12]. Moreover, it was shown that plasma half-life (19 hours) and fractional clearance rates of CRP were nearly constant in normal subjects, as well as in patients with infectious, inflammatory, and neoplastic conditions [13]. This marks CRP as a "precise objective index" of overall inflammatory activity and a surrogate of underlying cytokine stimulus [14].

Evidence from experimental and clinical studies has been accumulating that CRP may contribute directly to the pathogenesis of atherosclerosis and its complications through a variety of mechanisms.

(1) CRP binds to damaged cells and activates the complement system. This binding action means that CRP has a potential pathogenetic role in foam cell formation and in promoting atherosclerotic lesions [15]. Torzewski et al recently demonstrated that majority of foam cells be-

low the endothelium show positive staining for CRP, and there is a diffuse deposition of CRP in deep fibroelastic and fibromuscular layers of the intima with activated complement components [16]. CRP is also found deposited in the infarcted myocardium, together with activated complement components [17] and parenteral injection of CRP markedly enhances tissue damage, via a complement-dependent mechanism, in experimental myocardial infarction [15].

(2) CRP displays calcium-dependent in vitro binding and aggregation of low-density lipoprotein (LDL) and very LDL (VLDL) [18]. Bhakdi et al recently demonstrated that CRP binds to enzymatically degraded LDL particles and colocalizes with these lipid particles in early human atherosclerotic lesions [19].

(3) CRP is a potent stimulator of tissue factor production by monocytes [20], and the effect is augmented in the presence of other inflammatory mediators [21]. This interaction between CRP, inflammatory mediators, and tissue factor provides new insights into mechanisms linking inflammation and coagulation, which may contribute to the progression and outcome of atherosclerotic vascular diseases.

Several epidemiological studies and clinical observations have strengthened these possible pathogenetic associations between CRP and atherosclerosis and its complications. CRP was associated with the degree of atherosclerosis in coronary, peripheral, and extracranial brain arteries [22]. High CRP levels were significantly linked to future event risk in stable [23] and unstable [24, 25] angina patients. Breakthrough clinical evidence for CRP is established following prospective epidemiological studies among apparently healthy adults [26–29]. In the U.S. Physicians' Health Study, Ridker et al showed that men with CRP levels in the highest quartile had a threefold increase in the risk of developing a myocardial infarction (relative risk 2.9, $P < 0.001$) and twice the risk of developing a stroke (relative risk 1.9, $P = 0.02$) compared with men with levels in the lowest quartile. These risk estimates were found to be stable over an 8- to 10-year follow-up and were independent of other cardiovascular risk factors [27]. In many of these studies, CRP was associated with other known cardiovascular risk factors, such as increasing age, smoking, fibrinogen levels, and plasma lipids [26]. CRP, however, remains an independent and strong predictor for cardiovascular disease even after adjusting for these confounding factors. CRP also appears to be a more powerful risk factor for coronary artery disease than lipid-type risk factors [30, 31].

An invaluable way of confirming an association between elevated CRP and atherogenesis is disclosing a therapeutic challenge that controls APR, and hence CRP production, or one that prevents the proinflammatory actions of CRP. This is very difficult to achieve as there is no single factor controlling CRP secretion and molecular structure–function relationships of CRP have just become clarified [32]. However, there is indirect evidence that the classic treatments used in preventing cardiovascular diseases may act through mechanisms interfering with inflammatory mechanisms and CRP [9, 27, 33, 34]. In the U.S. Physicians' Health Study, the use of aspirin was associated with a significant reduction in the risk of myocardial infarction among men in the highest quartile of CRP (55.7%) compared with those in the lowest quartile (13.9%) [49]. In a secondary prevention trial, it was shown that pravastatin treatment significantly attenuates the effect of inflammation on cardiovascular risk [33]. Long-term follow-up of these patients (5 years) revealed that pravastatin resulted in a significant reduction in CRP levels (21.6% reduction in median CRP, $P = 0.007$) compared with those on placebo [34].

CRP, ESRD, AND ATHEROSCLEROSIS

C-reactive protein, in accord with its classic role, is used as a marker of infection or activity parameter of ongoing inflammatory disease in ESRD patients. Several observations during the last decade, however, have demonstrated that CRP is elevated in a significant proportion of ESRD patients without any apparent reason (Table 1). The first observation by Sethi et al showed that CRP was elevated in one third of the HD patients. In this study, CRP was correlated with the length of time on dialysis but remained unchanged during a single dialysis session [35]. Later studies reported controversial results for the correlations between CRP, length of time on dialysis, and dialysis session [36, 45, 46]. Haubitz, Schulze, and Koch, by using a sensitive CRP assay, showed a significant increase 24 hours after a dialysis session. As CRP levels usually increase 8 to 12 hours after the initial insult, the methodology of this study is more relevant than immediate measurements [47].

C-reactive protein elevation is not only limited to the HD population. Elevated CRP levels were reported in ESRD patients on either conservative treatment or peritoneal dialysis (PD; Table 1). Haubitz et al showed that highest values were in HD patients compared with PD or conservative treatment groups [48], whereas Kaysen observed that CRP levels were significantly greater in PD patients than in HD patients (unpublished observations) [49]. In contrast to an earlier study [36], several studies have demonstrated significantly elevated CRP levels in ESRD patients on conservative treatment [42, 46, 48, 50]. Interestingly, in one of these studies, serum samples obtained from eight individual patients 6, 12, and 18 weeks after the initiation of chronic HD treatment showed a significant increase in CRP levels compared with levels before starting HD [48].

Table 1. A chronological summary of clinical studies that assessed elevated C-reactive protein (CRP) prevalence in end-stage renal disease (ESRD) patients

Author	Year	Study group	Method[a]	Sensitivity (normal range)[b]	Patients with high CRP %
Sethi et al [35]	1988	99 (HD)	End-point immunonephelometry	5 mg/L (<10 mg/L)	35 (HD)
Docci et al [36]	1990	30 (C) 30 (CRF) 69 (HD)	Nephelometric immunoassay	2.7 mg/L (<5 mg/L)	40.6 (HD)
McIntyre et al [37]	1997	98 (HD) 68 (PD)	Immunoturbidometry	ND (<10 mg/L)	53 (HD) 25 (PD)
Quereshi et al [38]	1998	44 (C) 128 (HD)	Immunonephelometry	ND (10 mg/L)	53 (HD)
Owen et al [39]	1998	988 (HD)	Rate nephelometry	ND (<8 mg/L)	35 (HD)
Noh et al [40]	1998	105 (PD)	End point nephelometry	ND (≤8 mg/L)	12 (PD)
Creed [41]	1998	112 (HD)	ND	ND (0–5 mg/L)	65 (HD)
Zimmermann et al [10]	1999	160 (C) 280 (HD)	Nephelometric immunoassay	ND (<8 mg/L)	46 (HD)
Stenvinkel et al [42]	1999	109 (CRF) 22 (C)	ND	10 mg/L (ND)	32 (CRF)
Iseki et al [43]	1999	163 (HD)	Turbimetric immunoassay	ND (<6 mg/L)	21 (HD)
Panichi et al [44]	2000	201 (HD)	Laser nephelometry	1 mg/L (0.1–4.0 mg/L)	47 (HD)

Abbreviations are: ND, no data; C, normal healthy control; CRF, predialysis chronic renal failure patients; HD, chronic hemodialysis patients; PD, peritoneal dialysis patients.

[a] As mentioned in the study

[b] All CRP values are expressed in terms of mg/liter

Potential sources of elevated CRP in ESRD

The uremic state is associated with an altered immune response. A wide variety of factors in ESRD and especially in HD are capable of stimulating monocyte/macrophages to induce cytokine release [51]. Several studies have shown that proinflammatory cytokines were increased in predialysis uremic patients, as well as dialysis patients [52–54]. This suggests that uremia per se may cause a proinflammatory status with ongoing APR [42]. In the heretofore established proinflammatory background of uremia, extracorporeal circulation of blood during each HD session may act as a fresh stimulus for APR. Exposure of circulating mononuclear cells to the dialysis membrane [55] or exposure of circulating blood to lipopolysaccharide on the dialysate site of the membrane is a potential source for increased cytokine levels [56].

The two earlier studies that assessed the role of dialysis membranes on CRP production yielded equivocal results [36, 45]. A recent crossover study measuring CRP levels 24 hours after a dialysis session demonstrated that CRP was significantly increased following HD with bioincompatible (cuprammonium) compared with a relatively biocompatible membrane (polysulfon) [57]. They also reported that patients who had undergone an ultrapure dialysis with cuprammonium membrane had similar patterns of increase in IL-6 and CRP. They suggested that the type of membrane, rather than the bacterial quality of the dialysate, was responsible for the induction of the APR during HD [57]. However, Panichi et al, in a large group of HD patients ($N = 201$), have demonstrated that values of CRP and IL-6 were significantly higher in patients undergoing hemodiafiltration with low exchange volumes. They proposed that backfiltration of bacteria-derived contaminants during dialysis (with high-permeability membranes or low-volume hemodiafiltration) may induce a chronic inflammatory state [44]. The limitations of both studies warrant further studies to determine whether one or both of these factors are operative in activating APR in HD.

Exposure of blood to dialysate or dialysis membranes may not be the sole source of inflammation, as half of the HD patients have a normal serum CRP level [49]. The highly skewed distribution of CRP as well as IL-6 suggests that patient-specific processes, such as the type of vascular access [58] or unrecognized infections [38], may also play a role in inciting an inflammatory response.

The source of elevated CRP in PD patients is not obvious, either. Libetta et al reported that PD patients had comparable levels of mononuclear cell activation, suggesting a bioincompatibility of peritoneal dialysate solutions [59]. Exposure of the peritoneal membrane to plasticizers found in dialysate or transperitoneal access is suggested as a probable source of inflammation in PD patients [49, 60].

Clinical significance of elevated CRP in ESRD

The presence of an elevated CRP in a significant number of ESRD patients, particularly the HD population, confirms the existence of chronically activated APR. Although it is usually a beneficial response, the untoward effects of excessive and enduring APR already have been defined in the general population [14]. Recent data from ESRD patients also showed that elevated CRP levels have significant associations with hypoalbuminemia,

Table 2. Summary of clinical studies that assessed elevated CRP as a predictor of clinical outcome in ESRD patients

Author	Year	Study group	Follow-up duration *months*	Outcome parameter	Outcome predictor
Bergström et al (abstract)	1995	128 (HD)	48	All-cause mortality	CRP
Owen et al [39]	1998	1054 (HD)	6	All-cause mortality	Alb, Cre, TLC, not CRP
Noh et al [40]	1998	106 (PD)	24	All-cause mortality	CRP, CVD, Hct
Ikizler et al [63]	1999	73 (HD)	15	Hospitalization	CRP, LBM
Zimmermann et al [10]	1999	280 (HD)	24	All-cause and cardiovascular mortality	CRP, age
Iseki et al [43]	1999	163 (HD)	84	All-cause mortality	CRP
Yeun et al [11]	2000	91(HD)	34	All-cause and cardiovascular mortality	CRP, age

Abbreviations are: Alb, albumin; Cre, creatinine; TLC, total lymphocyte count; CVD, cardiovascular disease; LBM, lean body mass; Hct, hematocrit.

malnutrition, erythropoietin resistance, and most notably increased morbidity and mortality in both HD and PD patients (Table 2) [61, 62].

In their preliminary observation, Bergström et al were first to show that elevated CRP was a strong predictor of mortality over one and three years in HD patients. CRP appeared to be an independent predictor of survival even after adjusting for other variables (abstract; Bergström et al, *J Am Soc Nephrol* 6:573, 1995). In an uncontrolled, observational analysis of 988 HD patients, Owen and Lowrie showed the association between CRP and nutritional measures, but were unable to find any relationship between CRP and the odds risk of death [39]. Ikizler et al, using hospitalization as an outcome marker of morbidity, showed that 15% of the patients were hospitalized in the lowest CRP quartile (values less than 0.2 mg/dL), whereas this number was increased to 48% in the highest quartile of CRP (higher than 1.4 mg/dL) [63].

Three recent studies showed that CRP was a significant and independent predictor of death in chronic HD patients. In a prospective cohort analysis of 288 HD patients, Zimmermann et al showed that all-cause and cardiovascular mortality was higher in patients with elevated CRP, being 31 and 16%, respectively. Moreover, patients in the highest quartile of CRP had a 4.6-fold and 5.5-fold higher risk of all-cause and cardiovascular mortality in comparison to patients in lowest quartile [10]. Iseki et al showed a poorer survival in patients with elevated CRP (5-year survival rate of 44.4%) compared with normal CRP (5-year survival rate of 82.5%) in a seven-year follow-up in 163 HD patients [43]. Yeun et al also identified CRP levels as the most powerful predictor of all-cause and cardiovascular mortality in 91 HD patients followed for 34 months. Patients with CRP levels in the highest quartile (>11.5 mg/L) had the lowest survival, with the survival curve becoming flatter as CRP levels decreased to 5.3 to 11.5 mg/L and lower values (Table 2) [11].

Although PD patients usually have lower CRP levels in comparison to HD, increased CRP also appears as an independent predictor of mortality in these patients. Noh et al observed that two-year patient survival among 106 PD patients was significantly lower in the elevated CRP group than in the normal CRP group (66.7 vs. 94.1%) [40].

CRP and cardiovascular disease in ESRD

In keeping with the literature from the general population, there are emerging data in patients with ESRD linking CRP and cardiovascular disease. CRP levels were found to be associated with various classic markers of cardiovascular disease, such as lipoprotein (a) [10, 46, 50], fibrinogen, and low high-density lipoprotein [10] in ESRD populations. Two cross-sectional studies demonstrated that elevated CRP levels were associated with surrogate markers for atherosclerotic vascular disease in both HD [41] and predialysis [42] patients. Cardiovascular Risk Extended Evaluation in Dialysis (CREED) investigators showed that CRP was an independent predictor of the number of atherosclerotic plaques in carotid arteries of 112 chronic HD patients [41]. Stenvinkel et al detected a significantly increased intima-media thickness in carotid arteries of predialysis patients with CRP levels $\geq$10 mg/L (20.1 $\pm$ 1.0 mm^2) compared with those with CRP <10 mg/L (17.5 $\pm$ 0.6 mm^2, $P < 0.05$). An additional observation in this study was significantly positive correlation between CRP and oxidized LDL levels [42]. This suggests a possible relationship between increased oxidative stress in ESRD and inflammation, which warrants further studies to elucidate a "causal" interference.

Two prospective studies have extended this link between CRP and surrogate markers of atherosclerosis to cardiovascular mortality in HD patients [10, 11]. Zimmerman et al found that cardiovascular mortality was significantly increased with each increasing quartile of CRP, the highest quartile having a relative risk of 5.48 [10]. Yeun et al observed a similar association between CRP and cardiovascular mortality. In the Cox proportional hazard model, only CRP and age remained as predictors of cardiovascular mortality rather than other traditional risk factors [11].

CONCLUSION

There is a clear link between CRP and cardiovascular disease in general population. Emerging data from ESRD

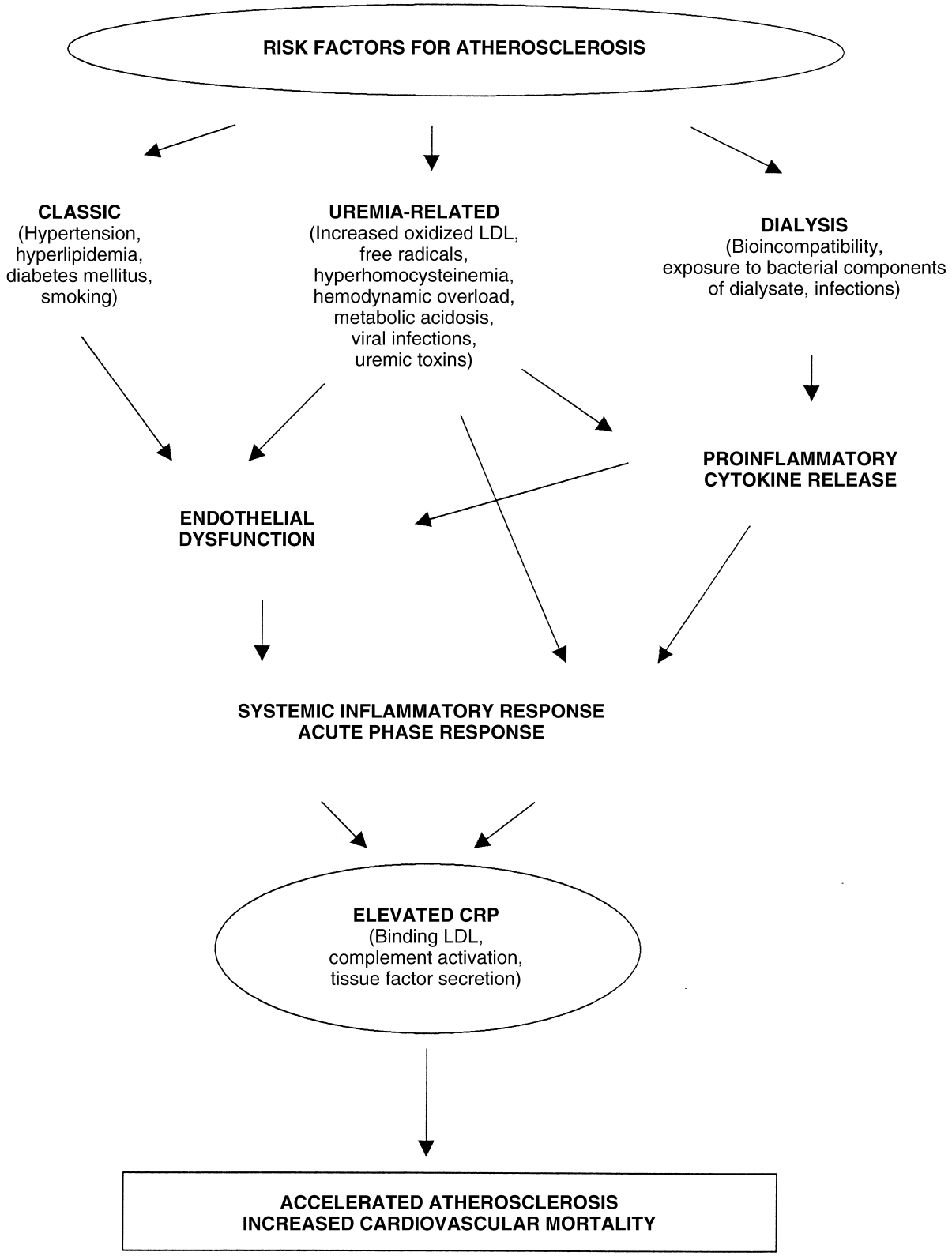

Fig. 2. Interrelationship between classic and uremia-related risk factors for atherosclerosis and the C-reactive protein (CRP). CRP is proposed to have a midway location in the complex events leading to accelerated atherosclerosis in uremia.

patients summarized previously in this article also indicate the possible link between elevated CRP levels, surrogate markers of atherosclerosis, and all-cause and cardiovascular mortality. Furthermore, there are a number of biologically plausible mechanisms that CRP might participate in the process of atherosclerosis. CRP therefore may be operative in the accelerated atherogenesis of uremic patients who have an established inflammatory environment. Undoubtedly, CRP is not the only factor mediating the whole cascade of events linking inflammation to atherosclerosis. However, it is a well-established marker of underlying cytokine burden, and the assay techniques for CRP are reliable, fully automated, and widely available. Given the links between elevated CRP and malnutrition, erythropoietin resistance, and clinical outcome parameters, CRP should be a routine investigation in ESRD patients.

In conclusion, research interest focused on understanding the role of CRP and inflammation as well as the associated risk factors may contribute to a better understanding the problem of cardiovascular morbidity and mortality in ESRD patients. In the puzzling milieu of uremia and dialytic treatments, CRP could have a midway position between traditional and uremia-related cardiovascular risk factors and atherosclerotic vascular disease (Fig. 2). Further research involvement will help to uncover the complex interactions between ESRD, inflammation, and atherosclerosis and should focus on (*1*) the underlying causes of inflammation, including significance of chronic infections ensuing with increased CRP levels, (*2*) the synergism between elevated CRP and other risk factors in preceding and promoting of atherosclerosis, and (*3*) the preventive measures to control APR, elevation of CRP, and/or inhibiting its proinflammatory character.

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REFERENCES

1. Lindner A, Charra B, Sherrard DJ, *et al*: Accelerated atherosclerosis in prolonged maintenance hemodialysis. *N Engl J Med* 290:667–671, 1974
2. Ross R: Atherosclerosis: An inflammatory disease. *N Engl J Med* 340:115–126, 1999
3. Lowrie EG, Lazarus JM, Hampers CL, *et al*: Cardiovascular disease in dialysis patients. *N Engl J Med* 290:737–738, 1974
4. Lazarus JM, Lowrie EG, Hampers CL, *et al*: Cardiovascular disease in uremic patients on hemodialysis. *Kidney Int* 7(Suppl):S167–S175, 1975
5. Foley RN, Parfrey PS, Sarnak MJ: Clinical epidemiology of cardiovascular disease in chronic renal failure. *Am J Kidney Dis* 32(Suppl 3):112–119, 1998
6. London GM, Drüeke TB: Atherosclerosis and arteriosclerosis in chronic failure. *Kidney Int* 51:1678–1695, 1997
7. Ridker PM: Evaluating novel cardiovascular risk factors: Can we do better predict heart attacks? *Ann Intern Med* 130:933–937, 1999
8. Lagrand WK, Visser CA, Hermens WT, *et al*: C-reactive protein as a cardiovascular risk factor: More than an epiphenomenon? *Circulation* 100:96–102, 1999
9. Morrow DA, Ridker PM: C-reactive protein, inflammation, and coronary risk. *Med Clin North Am* 84:149–161, 2000
10. Zimmermann J, Herrlinger S, Pruy A, *et al*: Inflammation enhances cardiovascular risk and mortality in hemodialysis patients. *Kidney Int* 55:648–658, 1999
11. Yeun JY, Levine RA, Mantadilok V, *et al*: C-reactive protein predicts all-cause and cardiovascular mortality in hemodialysis patients. *Am J Kidney Dis* 35:469–476, 2000
12. Pepys MB, Baltz ML: Acute phase proteins with special reference to C-reactive protein and related proteins (pentaxins) and serum amyloid a protein. *Adv Immunol* 34:141–212, 1983
13. Vigushin DM, Pepys MB, Hawkins PN: Metabolic and scintigraphic studies of radioiodinated human C-reactive protein in health and disease. *J Clin Invest* 91:1351–1357, 1993
14. Pepys MB: The acute phase response and C-reactive protein, in *Oxford Textbook of Medicine* (vol 2, 3rd ed), edited by Weatherall DJ, Ledingham JGG, Warrell DA, Oxford, Oxford University Press, 1996, pp 1527–1533
15. Griselli M, Herbert J, Hutchinson WL, *et al*: C-reactive protein and complement are important mediators of tissue damage in acute myocardial infarction. *J Exp Med* 190:1733–1739, 1999
16. Torzewski J, Torzewski M, Bowyer DE, *et al*: C-reactive protein frequently colocalizes with the terminal complement complex in the intima of early atherosclerotic lesions of human coronary arteries. *Arterioscler Thromb Vasc Biol* 18:1386–1392, 1998
17. Lagrand WK, Niessen HWM, Wolbink GJ, *et al*: C-reactive protein colocalizes with complement in human hearts during acute myocardial infarction. *Circulation* 95:97–103, 1997
18. Pepys MB, Rowe IF, Baltz ML: C-reactive protein: Binding to lipids and lipoproteins. *Int Rev Exp Pathol* 27:83–111, 1985
19. Bhakdi S, Torzewski M, Klouche M, *et al*: Binding of CRP to degraded, nonoxidized LDL enhances complement activation. *Arterioscler Thromb Vasc Biol* 19:2348–2354, 1999
20. Cermak J, Key NS, Bach RR, *et al*: C-reactive protein induces human peripheral blood monocytes to synthesize tissue factor. *Blood* 82:513–520, 1993
21. Nakagomi A, Freedman SB, Geczy CL: Interferon-γ and lipopolysaccharide potentiate monocyte tissue factor induction by C-reactive protein: Relationship with age, sex, and hormone replacement treatment. *Circulation* 101:1785–1791, 2000
22. Heinrich J, Schulte H, Schönfeld R, *et al*: Association of variables of coagulation, fibrinolysis and acute-phase with atherosclerosis in coronary and peripheral arteries and those arteries supplying the brain. *Thromb Haemostas* 73:374–379, 1995
23. Haverkate F, Thompson SG, Pyke SDM, *et al*: Production of C-reactive protein and risk of coronary events in stable and unstable angina. *Lancet* 349:462–466, 1997
24. Berk BC, Weintraub WS, Alexander RW: Elevation of C-reactive protein in "active" coronary artery disease. *Am J Cardiol* 65:168–172, 1990
25. Liuzzo G, Biasucci LM, Gallimore JR, *et al*: The prognostic value of C-reactive protein and serum amyloid A protein in severe unstable angina. *N Engl J Med* 331:417–424, 1994
26. Mendall MA, Patel P, Ballam L, *et al*: C reactive protein and its relation to cardiovascular risk factors: A population based cross sectional study. *BMJ* 312:1061–1065, 1996
27. Ridker PM, Cushman M, Stampfer MJ, *et al*: Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. *N Engl J Med* 336:973–979, 1997
28. Koenig W, Sund M, Frohlich M, *et al*: C-reactive protein, a sensitive marker of inflammation, predicts future risk of coronary heart disease in initially healthy middle-aged men: Results from the MONICA (Monitoring trends and determinants in cardiovascular disease) Augsburg cohort study, 1984 to 1992. *Circulation* 99:237–242, 1999
29. Ridker PM, Hennekens CH, Buring JE, *et al*: C-reactive protein

and other markers of inflammation in the prediction of cardiovascular disease in women. *N Engl J Med* 342:836–843, 2000
30. Mendall MA: C-reactive protein response and progression of atherosclerosis: Is atherosclerosis the byproduct of systemic infection? *Cardiologia* 42:1139–1144, 1997
31. Ridker PM, Glynn RJ, Hennekens CH: C-reactive protein adds to the predictive value of total and HDL cholesterol in determining risk of first myocardial infarction. *Circulation* 97:2007–2011, 1998
32. Thompson D, Pepys MB, Wood SP: The physiological structure of human C-reactive protein and its complex with phosphocholine. *Structure* 7:169–177, 1999
33. Ridker PM, Rifai N, Pfeffer MA, *et al*: Inflammation, pravastatin, and the risk of coronary events after myocardial infarction in patients with average cholesterol levels. *Circulation* 98:839–844, 1998
34. Ridker PM, Rifai N, Pfeffer MA, *et al*: Long-term effects of pravastatin on plasma concentration of C-reactive protein. *Circulation* 100:230–235, 1999
35. Sethi D, Muller BR, Brown EA, *et al*: C-reactive protein in haemodialysis patients with dialysis arthropathy. *Nephrol Dial Transplant* 3:269–271, 1988
36. Docci D, Bilancioni R, Buscaroli A, *et al*: Elevated serum levels of C-reactive protein in hemodialysis patients. *Nephron* 56:364–367, 1990
37. McIntyre C, Harper I, Macdougall IC, *et al*: Serum C-reactive protein as a marker for infection and inflammation in regular dialysis patients. *Clin Nephrol* 48:371–374, 1997
38. Quereshi AR, Alvestrand A, Danielsson A, *et al*: Factors predicting malnutrition in hemodialysis patients: A cross-sectional study. *Kidney Int* 53:773–782, 1998
39. Owen WF, Lowrie EG: C-reactive protein as an outcome predictor for maintenance hemodialysis patients. *Kidney Int* 54:627–636, 1998
40. Noh H, Lee SW, Kang SW, *et al*: Serum C-reactive protein: A predictor of mortality in continuous ambulatory peritoneal dialysis patients. *Perit Dial Int* 18:387–394, 1998
41. CREED (Cardiovascular Risk extended Evaluation in Dialysis Patients) Investigators: C-reactive protein and atherosclerosis in dialysis patients. *Nephrol Dial Transplant* 13:2710–2711, 1998
42. Stenvinkel P, Heimburger O, Paultre F, *et al*: Strong association between malnutrition, inflammation and atherosclerosis in chronic renal failure. *Kidney Int* 55:1899–1911, 1999
43. Iseki K, Tozawa M, Yoshi S, *et al*: Serum C-reactive protein (CRP) and risk of death in chronic dialysis patients. *Nephrol Dial Transplant* 14:1956–1960, 1999
44. Panichi V, Migliori M, De Pietro S, *et al*: Plasma C-reactive protein in hemodialysis patients: A cross sectional, longitudinal clinical survey. *Blood Purif* 18:30–36, 2000
45. Honkanen E, Gronhagen-Riska C, Teppo A-M, *et al*: Acute-phase proteins during hemodialysis: Correlations with serum interleukin-1β levels and different dialysis membranes. *Nephron* 57:283–287, 1991
46. Kario K, Matsuo T, Kobayashi H, *et al*: High lipoprotein(a) levels in chronic hemodialysis patients are closely related to the acute phase reaction. *Thromb Haemost* 74:1020–1024, 1995
47. Haubitz M, Schulze M, Koch KM: Increase of C-reactive protein serum values following haemodialysis. *Nephrol Dial Transplant* 5:500–503, 1990
48. Haubitz M, Brunkhorst R, Wrenger E, *et al*: Chronic induction of C-reactive protein by hemodialysis, but not by peritoneal dialysis therapy. *Perit Dial Int* 16:158–162, 1996
49. Kaysen GA: Inflammation, nutritional state and outcome in end stage renal disease. *Miner Electrolyte Metab* 25:242–250, 1999
50. Stenvinkel P, Heimburger O, Tuck CH, *et al*: Apo(a)-isoform size, nutritional status and inflammatory markers in chronic renal failure. *Kidney Int* 53:1336–1342, 1998
51. Dinarello CA: Cytokines: Agents provocateurs in hemodialysis? *Kidney Int* 41:683–694, 1992
52. Herbelin A, Urena P, Nguyen AT, *et al*: Elevated circulating levels of interleukin-6 in patients with chronic renal failure. *Kidney Int* 39:954–960, 1991
53. Cavaillon J-M, Poignet J-L, Fitting C, *et al*: Serum interleukin-6 in long-term hemodialyzed patients. *Nephron* 60:307–313, 1992
54. Pereira BJG, Shapiro L, King AJ, *et al*: Plasma levels of IL-1β, TNFα and their specific inhibitors in undialyzed chronic renal failure, CAPD and hemodialysis patients. *Kidney Int* 45:890–896, 1994
55. Zaoui P, Hakim RM: The effects of the dialysis membrane on cytokine release. *J Am Soc Nephrol* 4:1711–1718, 1994
56. Lonnemann G, Haubitz M, Schindler R: Hemodialysis-associated induction of cytokines. *Blood Purif* 8:214–222, 1990
57. Schouten WEM, Grooteman MPC, van Houte A-J, *et al*: Effects of dialyser and dialysate on the acute phase reaction in clinical bicarbonate dialysis. *Nephrol Dial Transplant* 15:379–384, 2000
58. Kaysen GA, Stevenson FT, Depner TA: Determinants of albumin concentration in hemodialysis patients. *Am J Kidney Dis* 29:658–668, 1997
59. Libetta C, de Nicola L, Rampino T, *et al*: Inflammatory effects of peritoneal dialysis: Evidence of systemic monocyte activation. *Kidney Int* 49:506–511, 1996
60. Gabay C, Kushner I: Acute-phase proteins and other systemic responses to inflammation. *N Engl J Med* 340:448–454, 1999
61. Bergström J, Lindholm B: Malnutrition, cardiac disease, and mortality: An integrated point of view. *Am J Kidney Dis* 32:834–841, 1998
62. Lowrie EG: Acute-phase inflammatory process contributes to malnutrition, anemia, and possibly other abnormalities in dialysis patients. *Am J Kidney Dis* 32(Suppl 4):S105–S112, 1998
63. Ikizler TA, Wingard RL, Harvell J, *et al*: Association of morbidity with markers of nutrition and inflammation in chronic hemodialysis patients: A prospective study. *Kidney Int* 55:1945–1951, 1999