Persistent Inflammation as a Catalyst for Other Risk Factors in Chronic Kidney Disease: A Hypothesis Proposal

Juan Jesús Carrero*† and Peter Stenvinkel*

*Division of Renal Medicine, Department of Clinical Science, Intervention and Technology, and †Department of Molecular Medicine and Surgery, Center for Molecular Medicine, Karolinska Institutet, Stockholm, Sweden

Because inflammation by now is a “traditional” finding that predicts poor outcome and cardiovascular events in the vast majority of patients with ESRD, it could be argued that inflammatory biomarkers should no longer be considered “novel” risk factors. In this review, we forward the hypothesis that, in addition to putative direct proatherogenic effects, persistent inflammation may serve as a catalyst and, in the toxic uremic milieu, modulate the effects of other concurrent vascular and nutritional risk factors. We discuss some recent observational studies, suggesting that the presence of persistent inflammation magnifies the risk for poor outcome via mechanisms related to self-enhancement of the inflammatory cascade and exacerbation of both the wasting and the vascular calcification processes. Because persistent inflammation may be the silent culprit of other commonly observed pathophysiologic alterations in chronic kidney disease, it is imperative that inflammatory markers be regularly monitored and therapeutic attempts be made to target persistent low-grade inflammation in this patient group.


Since more than 10 yr, the consequences of systemic inflammation have gained attention in nephrology. In fact, this “novel” risk factor, a decade later, has emerged as a “traditional” finding in the majority of epidemiologic studies of patients with chronic kidney disease (CKD). Inflammation (Latin inflammatio, to set on fire) may be defined as a complex biologic response of vascular tissues to harmful stimuli, such as pathogens, damaged cells, or irritants. Inflammation should be regarded as a protective attempt by the organism to remove the injurious stimuli as well as to initiate the healing process for the tissue. Although the release of proinflammatory cytokines may have acute beneficial effects, chronic systemic elevation is likely to produce detrimental effects. Indeed, this is the problem faced in CKD, in which a state of persistent low-grade inflammation is commonly observed. Chronic inflammation is characterized by the persistent effect of a causative stimulus, which leads to destruction of cells and tissues and has deleterious effects to the body. In CKD, especially in ESRD, the systemic concentrations of both pro- and anti-inflammatory cytokines are several-fold higher as a result of both decreased renal clearance and increased production. Several factors, both dialysis-related (e.g., membrane bioincompatibility) and non–dialysis-related (e.g., infection, comorbidity, genetic factors, diet), may additionally contribute to a state of persistent inflammation (1).

There is a steady body of evidence concerning the robustness of single measurements of various inflammatory biomarkers, such as C-reactive protein (CRP), IL-6, fibrinogen, pentraxin-3, S-albumin, and white blood cell count, as independent predictors of mortality in patients with CKD (2). Despite that many comparative studies on prognostic performance suggest that IL-6 may be the best outcome predictor in early and advanced CKD (3), CRP in the clinical setting has aroused as the prototypic marker of inflammation as a result of its reliability, low cost, and availability (1); however, although CRP reflects systemic inflammation and predicts cardiovascular risk, it does not seem to promote vascular disease. Indeed, although recent studies showed that CRP haplotypes predicted CRP levels, an association to cardiovascular disease (CVD) was observed in neither nonrenal (4) nor dialysis (5) patients. Because CRP is a moving target and levels fluctuate over time, being mainly influenced by processes such as transient infections and comorbidity, continuous monitoring of CRP is recommended because it provides more precise information on the “real” inflammatory state (6).

In contrast to variations in the CRP gene, IL-6 gene polymorphisms seem to be important genetic factors in premature coronary artery disease (7). Thus, IL-6 may directly act as a promoter of atherosclerosis and wasting by actively participating in the processes of vascular calcification, muscle catabolism, oxidative stress, anorexia, cell aging, hormonal derangements, and endothelial dysfunction (2,8–10). In this review, we propose the hypothesis that in addition to putative direct proatherogenic effects, persistent inflammation may serve as a catalyst and, in the uremic milieu, modulate the effects of risk factors for wasting and vascular disease. Indeed, we recently observed studies indicating that, in the presence of persistent inflammation, the effects of biochemical alterations and genetic susceptibilities become exacerbated; however, it should be emphasized that some of the examples discussed here are secondary observations, and because of lower samples size when analyzing subgroups, interaction tests have not always been applied. Various statistical methods exist to denote interaction on the basis of multiplicative or additive tests. For a causal
interpretation, interaction is usually measured on an additive scale (11). A correct use of these epidemiologic tools may help us to weigh the magnitude of risk modification.

**Inflammatory Milieu Synergistically Stimulates Cytokine Production**

In analogy to the saying, “Money goes where money is,” activated macrophages and leukocytes migrate to existing sites of inflammation to stimulate further the proinflammatory milieu. Cytokines interact with each other in complex ways that may be additive, synergistic, or antagonistic or may involve the induction of subsequent cascades of cytokines and other messenger substances (12,13). If cytokines synergistically induce each other’s expression, then their effects may also be synergistically multiplied, specifically the effect of persistent inflammation on mortality. In the uremic milieu, in which cytokines are retained as a result of loss of residual renal function and stimulated by comorbidity and the dialysis procedure per se, such interactions should be of relevance. Indeed, Liu et al. (14) showed that concomitant carriers of two single-nucleotide polymorphisms in the genes coding for IL-6 and TNF-β multiplicatively increased the risk both for CVD and for CVD mortality. Unlike the measurements of serum levels of IL-6 and TNF-β that are strongly correlated, the variants of both genes are uncorrelated because they reside on different chromosomes and thereby provide an option to examine their independent effects. Because TNF-β acts as a primary proinflammatory cytokine that stimulates the expression of IL-6, this gene–gene interaction suggests that TNF-β may have protherogenic effects in addition to its effect on IL-6 production.

An inflammation–inflammation exacerbation of the mortality risk is found not only at a genetic but also at a cellular level. For instance, migration of monocytes into the vessel wall contributes to the onset and progression of atherosclerosis. Both in vitro and animal studies suggested a selective role of distinct monocyte subpopulations in the development of atherosclerosis (15). In dialysis patients, Heine et al. (16) showed that CD14\(^{++}\)CD16\(^{+}\) monocytes but not total monocyte numbers predicted cardiovascular events. In that study, across increasing CRP and CD14\(^{++}\)CD16\(^{+}\) monocyte tertiles, the death count became increasingly higher (Figure 1A). This led the authors to hypothesize that low-grade persistent inflammation exacerbates the effect of activated monocytes on adverse outcomes. In accordance, we studied whether increased soluble CD14 levels, in the presence of an elevated inflammatory milieu, may relate to an exacerbation of the mortality risk (17). Although we could observe gradual increases in hazard ratios and death counts, this effect was not strong enough to denote a statistical interaction because of the multiplicity of effects. Nonetheless, although both studies are restricted by a low sample size, they suggest a catalytic effect of proinflammatory cytokines and activated monocytes on adverse outcome in ESRD.

The infiltration of monocytes and T lymphocytes in the vascular wall depends on the response to chemokines, and CD14\(^{++}\)CD16\(^{+}\) monocytes are characterized by a unique pattern of chemokine receptors, represented by the chemokine receptor 5 (CCR5). In states of inflammation, CCR5 could contribute to atherogenesis through the binding of its ligands, which in turn mediate the recruitment of inflammatory cells to the endothelium. It is interesting that patients with arteriosclerosis and a dysfunctional CCR5 as a result of the gene polymorphism CCR5 deletion 32 (CCR5Δ32) have an improved prognosis (18). In accordance, Muntinghe et al. (19) demonstrated that CCR5Δ32 might be a rate-limiting factor in the increased mortality rate associated with systemic inflammation in incident dialysis patients. Because a CCR5Δ32 polymorphism attenuated the adverse effects of an inflammatory state on overall and cardiovascular mortality, this antagonistic gene–environment interaction illustrates the cross-talk among inflammatory cells. It can also be speculated that uremia is associated with a loss of phenotypic plasticity (i.e., the toxic uremic milieu put on an environmental pressure that unmasks underlying genetic differences).

Persistent uremic inflammation may also serve as a catalyst and increase the sensitivity and/or risk to various infectious agents, such as *Chlamydia pneumoniae* seropositivity. *C. pneumoniae* seropositivity has been shown to stimulate IL-6 production, and both features are present in dialysis patients with progres-
sive carotid artery atherosclerosis (20). A recent study by Kim et al. (21) demonstrated that elevated IL-6 levels in dialysis patients with C. pneumoniae aggravated the atherosclerotic progression of the carotid artery (Figure 1B). Their findings indicate that C. pneumoniae not only may trigger the production of this proinflammatory atherogenic cytokine, but also accelerate the process of atherosclerosis only in the presence of inflammation. Thus, the serologic assay of C. pneumoniae combined with the measurement of IL-6 could be of help in predicting the progression of atherosclerosis in ESRD.

**Inflammation Exacerbates the Effects of Protein-Energy Wasting**

The observation that both protein-energy wasting (PEW) and persistent inflammation are highly prevalent in patients with ESRD and are associated with a substantially increased mortality risk has generated much interest. Because PEW, inflammation, and atherosclerotic CVD often coexist in the uremic milieu, these risk factors are linked (22). Indeed, it seems that proinflammatory cytokines synergistically augment the deleterious effects that lead to PEW and that both inflammation and PEW exacerbate the mortality risk. One of the main detrimental effects of proinflammatory cytokine activation in patients with ESRD is muscle depletion (23). Increased amino acid demand or amino acid depletion itself is unlikely to be the sole catabolic signal for protein breakdown during hemodialysis (HD). Instead, IL-6 activation seems to override the anabolic response to amino acid supplementation (24). Besides, the IL-6 release from muscle during proteolysis may further stimulate the whole catabolic process in a vicious circle (25). In addition, a synergism between IL-6 and other catabolic substances that produce muscle loss have recently been demonstrated. First, Zhang et al. (26) demonstrated a previously unrecognized role for serum amyloid A in acting synergistically with IL-6 to impair insulin/IGF-1 signaling by increasing SOCS3 transcription, which results in muscle proteolysis (Figure 2A). They proposed that angiotensin II may stimulate an interaction between the liver and the skeletal muscle because the liver becomes the major source of IL-6 and serum amyloid A. Second, elevated IL-6 and soluble TNF-like weak inducer of apoptosis (TWEAK) levels have additive effects on outcome prognostication (Figure 2B) (27). TWEAK is a member of the TNF superfamily, which through binding to its receptor Fn14 mediates various biologic effects, including exacerbation of the inflammatory response and muscle-wasting activation through the ubiquitin-proteasome and NF-κB pathways (28). Furthermore, because IL-6 induces the production of Fn14, it has been suggested that a persistently inflamed state may exacerbate the action of TWEAK through increased receptor synthesis (29). Thus, as we observed that simultaneously elevated levels of TWEAK and IL-6 in dialysis patients were associated with significant reductions in IGF-1 and handgrip strength, this combination may lead to muscle catabolism (27).

Resistance to the anabolic drive by the growth hormone (GH)/IGF-1 axis may constitute another factor that contributes to the loss of strength and muscle mass in patients with CKD. Although several clinical studies have reported that GH has a salutary effect on body composition and muscle protein synthesis in patients with CKD (30), the responses to GH treatment vary considerably (31). Because inflammation inhibits GH action (32), it can be postulated that the GH response is blunted in inflammatory conditions. Indeed, Garibotto et al. (33) found that whereas GH forearm perfusion caused a decrease in the negative potassium and protein balance of HD patients without inflammation, no such effect was seen in HD patients with inflammation. Their finding suggests that the resistance to pharmacologic dosages of GH is not related to uremia per se but rather to inflammation.

Although inflammation may enhance the appearance of PEW, inflammation may also interact with CVD in exacerbating the mortality risk. A Dutch study demonstrated that the concurrent presence of inflammation and PEW produced a higher
mortality rate than expected from the solo effects of PEW and inflammation (34). Further inclusion of CVD to this model rendered a mortality rate of 16 deaths per 100 person-years higher than expected from their solo effects. Thus, their observation translates epidemiologic observations into evidence for the existence of a syndrome of PEW, inflammation, and atherosclerotic CVD whereby the whole is more than its parts (22). Moreover, Parekh et al. (35) found that although sudden cardiac death was common among patients with CKD, inflammation and malnutrition significantly increased its occurrence independent of traditional cardiovascular risk factors. Specifically, across increasing CRP tertiles cross-classified with decreasing S-albumin tertiles, an exacerbation of sudden cardiac death risk was observed.

**Inflammation as a Catalyst of the Vascular Calcification Process**

Increased vascular calcification is a major cause of increased morbidity and mortality in dialysis patients (36,37). Vascular calcification is an active cell-mediated process and likely reflects a transformation of vascular smooth muscle cells to osteoblast-like cells. Concomitant factors, such as inflammation and/or increased oxidative stress, may directly stimulate the vascular calcification process. For instance, TNF-α can induce mineralization of calcifying vascular cells in vitro (38), and co-culture of these cells with monocyte/macrophages can accelerate mineralization (39). Several recent studies suggested that systemic inflammation and markers of mineral metabolism act in concert to promote accelerated vascular calcification. Osteoprotegerin (OPG), a member of the TNF-α receptor superfamily, inhibits osteoclastogenesis, osteoclast activation, and osteoclast-like formation in arteries and atherosclerotic plaques. Because Morena et al. (40) showed that OPG is associated with vascular calcification and mortality in dialysis patients, their findings seem to contradict the calcification inhibitory properties of this protein. Elevated OPG levels have been interpreted as a failed compensatory mechanism trying to counteract the ongoing calcification process; however, because OPG production and expression are highly regulated by several inflammatory cytokines (41), it could also be speculated that increased OPG levels in CKD may in part be a consequence of systemic inflammation (42). Indeed, Morena et al. (40) showed that whereas elevated OPG in the context of an inflammatory milieu strongly predicted survival, such effect was not observed in dialysis patients without inflammation and with elevated OPG.

We recently confirmed their finding in a larger cohort of 265 incident dialysis patients (Figure 3B) (43). Because both RANKL and OPG influence the inflammatory component of atherosclerosis (44) and OPG upregulates the endothelial cell adhesion molecule response to TNF-α (45), this suggests a mechanism by which OPG may stimulate inflammation in atheroma and thereby promote the progression and complications of atherosclerosis.

Fetuin-A, which plays a pivotal role in the inhibition of Ca × PO₄ precipitation process, is associated with both PEW and inflammation, because it acts a negative acute-phase reactant. In consequence, low levels of circulating fetuin-A are associated with increased cardiovascular burden and mortality (46); however, recent evidence suggests a synergism between persistent inflammation and low fetuin-A levels in the context of uremia. Whereas patients who had CKD and a genetic propensity for low fetuin-A levels had a higher mortality rate in the presence of inflammation (47), a significant prognostic value of low serum fetuin-A levels in HD patients was observed only in the presence of persistent inflammation (Figure 3A) (48). Taken together, an active interplay between vascular calcification and atherosclerosis via inflammation may exist, which particularly seems to catalyze this effect against a background of severe mineral disturbances.

**Inflammation-Catalyst Effect: A Hypothesis Proposal**

In summary, recent observational studies suggested that inflammation could serve as a catalyst and magnify the risk for poor outcome via mechanisms related to self-enhancement of the inflammatory cascade and/or exacerbation of both wasting and vascular calcification processes (Figure 4). Although a CRP level of ≥5 mg/L is considered to reflect inflammation in the general population, this value is below the CRP levels of most patients with CKD. Still lacking a clinical definition for uremic inflammation, we do not yet fully understand the implications of low-grade persistent inflammation in this patient group. Further studies need to elucidate whether persistent inflammation serves as a catalyst by sensing and converting the endothelium into a procoagulant and proinflammatory surface that...
makes the vasculature more vulnerable to the effects of other circulating risk factors. Such a scenario is supported by the strong documented associations between inflammatory markers and endothelial dysfunction in patients with CKD (49). Future prognostic and etiologic studies should take into consideration the risk effect modification that low-grade persistent inflammation may exert on their outcomes. Understanding how persistent low-grade inflammation amplifies risk may be the first step toward the implementation of novel therapeutic strategies. Despite more than 10 yr of inflammation-focused research, very little has been done regarding the effect of an anti-inflammatory intervention on uremic outcome. Recently and in contrast to the findings of the Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) (50) in a primary prevention study, the A study to evaluate the Use of Rosuvastatin in subjects On Regular haemodialysis: an Assessment of survival and cardiovascular events (AURORA) (51) showed that although rosuvastatin treatment lowered CRP levels significantly, no effects on cardiovascular events were observed in 2776 dialysis patients who were followed up for 3.8 yr. However, because inflammation may serve as a catalyst (and alter the risk profile), evaluation of the effects of statin on outcome, in our opinion, should be done separately in dialysis patients with and without inflammation. In the future, the putative effects of anti-inflammatory treatment strategies (e.g., targeted anticytokine therapies) need to be evaluated in the context of the possibility that inflammation, rather than being the culprit itself, may serve as a catalyst and sensitize the vasculature and/or muscle tissue to vascular and nutritional risk factors.

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