

Cytokine Dysregulation in Chronic Kidney Disease: How Can We Treat It?

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Key Words

Chronic kidney disease · Cytokine · Inflammation · Interleukin · Mortality · Dialysis

Abstract

As the kidney is the major site for elimination of many cytokines, the delicate equilibrium of pro-inflammatory cytokines and their inhibitors is clearly dysregulated in chronic kidney disease (CKD) patients. The consequences of the altered immune response in uremia lead to a state of persistent inflammation which is highly prevalent among CKD patients and is linked to complications such as the development of protein-energy wasting and atherosclerotic vascular disease. The present review aims at reviewing this complex orchestration of uremic cytokines beyond the well-studied interleukin-6 and tumor necrosis factor- α . Finally, we update our current understanding on anti-inflammatory treatment strategies in CKD patients, including nutritional and lifestyle measurements, pharmacological intervention and specific anticytokine strategies targeting the dialytic procedure.

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Introduction

In the immune system, a complex orchestration of cytokines and other molecules act in a paracrine, autocrine or endocrine fashion to control the differentiation, pro-

liferation and activity of immune cells. As the kidney is the major site for elimination of many of these cytokines, the delicate equilibrium of pro-inflammatory cytokines and their inhibitors is clearly dysregulated in chronic kidney disease (CKD) patients [1, 2]. The dialysis procedure [3] further stimulates circulating nuclear cells for cytokine production [4], making them respond more vigorously to exposure to endotoxins [5]. These consequences of the altered immune response in uremia lead to a state of persistent inflammation [6, 7] which is highly prevalent among CKD patients and is linked to complications such as the development of protein-energy wasting (PEW) and atherosclerotic vascular disease [3, 8]. Inflammation, PEW and atherosclerosis often coexist in CKD [9], and each of these risk factors independently predicts outcome in these patients. In order to understand this complex orchestration, selected cytokines will be reviewed with regards to our current understanding of the uremic cytokine misbalance, as well as an updated status of current and future anti-cytokine strategies in CKD.

Innate and Humoral Immune System: Keeping Homeostasis as a Principle

The cytokine response to infection or injury is a well-coordinated and precisely controlled process aimed at maintaining the body homeostasis. When addressing the

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role of cytokines in the context of atherosclerosis and uremia, it is important to distinguish between local and systemic inflammation. Locally produced pro-inflammatory mediators with atherogenic activity include interleukin (IL)-8, IL-12, IL-18, tumor necrosis factor (TNF)- α and interferon (IFN)- γ , and among systemic mediators and markers of inflammation IL-6 and IL-8 should be mentioned [10]. Cytokines are soluble proteins with low molecular weight that are produced in response to an antigen and other signals and function as chemical messengers regulating various aspects of the innate and humoral immune systems. They are produced by virtually all cells involved in innate and humoral immunity, but especially by T helper (Th) lymphocytes. CD4 T helper cells are classified into two distinct types. Th1 cells primarily produce several pro-inflammatory cytokines notably IFN- γ , IL-12 and TNF- α , which promote cellular immunity, whereas Th2 cells secrete a different set of cytokines, primarily IL-4, IL-5, IL-10 and IL-6, which promote humoral immunity. There is a T regulatory cell (CD4+/CD25-) that produces IL-10 and is capable of down-regulating both Th1 and Th2 responses. Th1 cytokines stimulate the synthesis of nitric oxide and other inflammatory mediators, the functional activity of T cytotoxic cells, natural killer (NK) cells and activated macrophages, exerting altogether a pro-inflammatory action. On the other hand, Th2 cytokines inhibit macrophage activation, T cell proliferation and the production of pro-inflammatory cytokines, being therefore involved in anti-inflammatory processes. Th1 and Th2 responses are mutually inhibitory. Thus, IL-12 and IFN- γ inhibit Th2, while IL-4 and IL-10 inhibit Th1 cell activities [10, 11]. Indeed, the balance between pro- and anti-inflammatory cytokines rather than the absolute amount might be crucial for the progression of the atherosclerotic lesion [12].

In order to properly understand the state of cytokine dysregulation that is present in the CKD patients, a number of considerations should be made involving cytokine measurements [13]. Firstly, most of the published studies concentrate on selected cytokines measured in plasma, culture supernatants or in association with circulating cells. However, cytokines are moving targets and counterbalanced by inhibitors or other cytokines with opposed effects. Secondly, cytokines rarely act alone because they stimulate a variety of cell types to produce and secrete other cytokines in a cascade fashion. Elevation of one cytokine immediately leads to up- or down-regulation of several others. As many of the effect of cytokines are local, not systemic, these paracrine effects of cytokines are hard to detect. Thirdly, pro- and anti-inflam-

matory cytokines bind to specific cytokine carriers (such as α_2 -macroglobulin) and these different binding proteins may serve as extracellular cytokine reservoirs and protective shields against degradation of cytokines. Thus, one important aspect that needs to be taken into account when understanding these studies is that established immunoassays to detect these cytokines cannot usually distinguish between active proteins and those that are blocked by their specific inhibitors.

Cytokine Dysregulation in Uremia: An Allostatic Condition

CKD is characterized by allostasis, i.e. a chronic state of disordered homeostasis that allows survival of the patients only at the expense of well-being and poor outcome. It is generally believed that uremia per se, while generally suppressing T cell function is also associated with altered Th balance. While one study suggests a Th1 predominance under uremic conditions [14], another report indicates a Th2 prevalence [15]. Clearly, further studies are needed to determine if alterations in Th balance may predispose to alterations in cytokines that might be responsible for the increased CVD risk in ESRD. It seems, however, that during the interdialytic interval, the cytokine production from monocytes is normal, although these cells release large amounts of pro-inflammatory cytokines under stimulation [16].

As a recent report from our group has extensively reviewed the role of IL-6, TNF- α and IL-10 [13], these cytokines which will not be contemplated in the present review. Perhaps among those, IL-6 may be the most studied cytokine in CKD, and it is becoming more apparent that this pro-inflammatory cytokine plays a key role in the pathogenesis of both PEW and atherosclerosis in the CKD and dialysis populations [17]. Some studies have recently tried to prospectively compare the predictive value of different inflammatory markers in dialysis patients. Two of them, one using receiver operator characteristics (ROC) curves [18] and one using multivariate modeling [19], showed that the predictive value of IL-6 levels was higher than that attributable to other molecules studied with regard to all-cause and cardiovascular mortality. Another recent comparative study based on ROC analysis also showed that the prediction power of the combined inflammatory burden of a number of commonly measured cytokines and adhesion molecules was identical to that provided by the sole measurement of IL-6 [20]. These results were further confirmed in another Brazil-

ian HD cohort [21]. Thus, as IL-6 seems to be the best option for risk stratification in dialysis patients, particularly in the context of clinical studies, further studies are needed to compare the predictive value of different inflammatory biomarkers also in patients with mild to moderate CKD. However, in clinical practice the acute-phase protein CRP is still the most commonly used biomarker of the degree of inflammation, and as CRP measurements are cheap, reliable and easily implanted, they are widely used in many countries around the world.

Interleukin-18

IL-18 is a pro-inflammatory cytokine formerly known as IFN- γ -inducing factor, which seems to be its primary immune action [22]. While IL-18 mRNA has been detected in keratinocytes, small intestine epithelial cells, adrenal cells, macrophages, pancreas, skeletal muscle, liver, lung and peripheral blood mononuclear cells, IL-18 receptors have been identified only on T, B and NK cells. IL-18 is a pro-atherogenic cytokine associated with the development of CVD [23]. Indeed, the IL-18 expression is increased in human atherosclerotic plaques and associated with plaque destabilization [24]. In a mice model, recombinant IL-18 injection leads to an increase in atherosclerotic lesions, possibly through enhancement of an inflammatory response involving an IFN- γ -dependent mechanism [25]. Elevated plasma IL-18 levels are present in a number of inflammatory diseases, including rheumatoid arthritis, Crohn's disease, atherosclerosis [26] and CKD [27]. IL-18 levels have been shown to be increased in predialysis, HD and peritoneal dialysis (PD) patients [23, 26, 28, 29]. As increased production of IFN- γ is one of the main characteristics of the Th1 response, IL-18 accumulation in uremic patients may contribute to such a response also in HD patients [26, 30]. A direct correlation between IL-18 levels and time on dialysis (dialysis vintage) was shown in both HD [28] and PD [23] patients, and may be ascribed to a chronic inflammatory state that progresses over time.

In stable and unstable angina patients, an elevated level of IL-18 was shown to be a strong predictor of cardiovascular mortality [31]. In HD patients, plasma IL-18 levels predicted hospitalization rate, but not mortality [32]. A similar finding was also shown in PD patients [23]. Indeed, the gain in prediction power to that of IL-6 associated with the inclusion of IL-18 was small and nonsignificant [19]. Interestingly, a recent study reported that the IL-18 levels were higher in PD patients as compared to predialysis patients and HD patients [33]. Consistent with this finding, IL-18 has been shown to be protective

during bacterial infections, and high IL-18 levels in peritoneal dialysate effluent during the early phase of peritonitis correlated with a predominant Th1 immune response and favorable outcome [34]. In light of these results, it could be speculated that local IL-18 production may be part of a protective early immune response to PD-related peritonitis.

Interleukin-12

IL-12 is another pro-inflammatory cytokine that has a central function in the initiation and regulation of the cellular immune response. It has the capacity to regulate the differentiation of native T cells into Th1 cells, which is crucial in determining resistance and the type of response that will be elicited in response to a particular pathogen. IL-12 is produced early in the infectious process by activated macrophages and enhances the host innate resistance at the same time as shaping the ultimate antigen-specific immune response [35]. IL-12 plays an important role mediating the enhancement of the cytotoxic activity of NK cells and CD8+ cytotoxic T lymphocytes. There also seems to be a link between IL-2 and the signal transduction of IL-12 in NK cells. Because of their synergistic roles in stimulating inflammation, IL-12, IFN- γ and TNF- α are considered to be major pro-inflammatory cytokines [11].

In general, IL-12 levels are increased in CKD patients with or without dialysis therapy [36–38], being involved in promoting a state of Th1 differentiation. In PD, local IL-12 production is part of a protective early immune response to peritonitis and correlates well with type 1 T cell polarization [34, 39]. In HD, the production of IL-12 by macrophages and of IFN- γ by Th1 cells seems to be higher as compared to controls [40]. Consequently, increased IL-12 levels were associated with improved survival in a large cohort of patients on dialysis [36]. However, the bioincompatibility of the HD procedure seems to play a role in IL-12 production which could worsen the uremic immunodeficiency, as HD patients dialyzed with cuprophane membranes have a lower IL-12 production than those using polymethylmethacrylate membranes or nondialyzed uremic patients [41].

Interleukin-7 and Interleukin-15

IL-7 is a hematopoietic growth factor – secreted by the stromal cells of the red marrow and thymus – capable of stimulating the proliferation of lymphoid progenitor cells. This cytokine is important for proliferation during certain stages of B cell maturation, and for T and NK cell survival, development and homeostasis. IL-15 is a cyto-

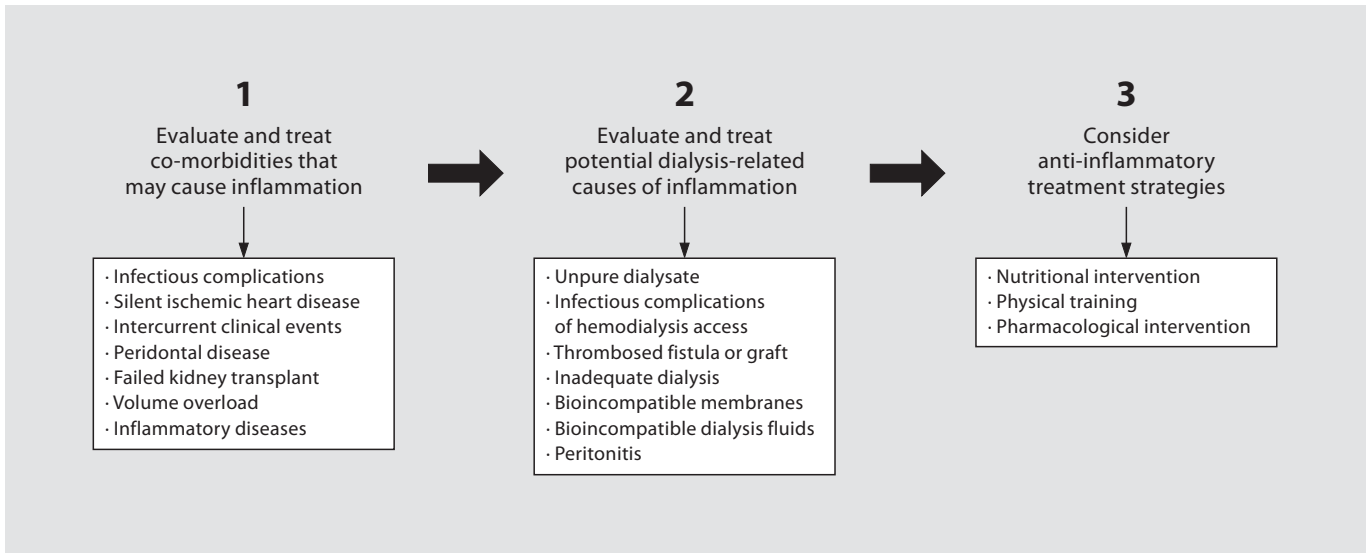


Fig. 1. Suggested steps to target persistent inflammation in CKD patients.

kine with structural similarity to IL-2 that is secreted mainly by mononuclear phagocytes following infection by viruses. This cytokine induces cell proliferation of NK cells; cells of the innate immune system whose principal role is to kill virally infected cells.

Plasma IL-7 concentrations have been reported to be decreased in CKD patients [42], which is interesting because virtually all the other cytokines seem to be increased in the uremic milieu [36]. This IL-7 deficiency has been related to lymphopenia in specific T cell subsets from CKD patients [42]. In isolated peripheral blood mononuclear cells (PBMCs) from HD patients the simultaneous stimulation with the combination TNF- α plus IL-15 appeared to be more potent than the stimulation of the cytokines alone [43]. Hausmann et al. [44] experimentally demonstrated that human peritoneal mesothelial cells (HPMCs) secrete IFN- γ , IL-2 and IL-15 upon antigen stimulation. Consequently, increased IL-15 levels were observed in effluents of PD patients suffering from peritonitis as compared to those free of peritonitis [44]. As IL-15 is a potent T cell activator [45], it is plausible that HPMCs may participate in the peritoneal immune response against invading pathogens by contributing to T cell activation through IL-15 secretion.

Interleukin-8

IL-8 is produced by macrophages and other cell types such as epithelial cells. When first encountering an antigen, macrophages are the first cells to respond, by phago-

cyting the particle. Upon processing, they release primarily IL-8 to signal to other immune cells to come to the site of inflammation. Thus, IL-8 serves as a chemical signal to attract neutrophils at the site of inflammation, and therefore it is also known as neutrophil chemotactic factor. IL-8 is a well-established pro-atherogenic cytokine [46]. In HD patients, IL-8 levels were dramatically increased, and constituted a powerful and independent predictive factor for cardiovascular and all-cause mortality [47]. As it has been suggested that anti-oxidant and reactive oxygen species (ROS) can up-regulate IL-8 gene expression [48], it is possible that the ROS up-regulation associated to HD contributes to the induction of IL-8 [49]. However, conflicting results exist to date, on whether a single HD session increases or decreases the concentration of IL-8 [50, 51]. Of interest, increasing doses of simvastatin to PBMC cultures from CKD patients induced a dose-dependent inhibition of both IL-6 and IL-8 [52, 53].

Implications for Cytokine Treatment Strategies

As the immune system is extremely complex and of great importance for maintaining homeostasis, urgent measures should be taken to counteract its deleterious effects (fig. 1). It should be logical to start by targeting the co-morbidities and dialytic processes that may cause inflammation (see below). Also, a number of putative anti-inflammatory strategies are available (table 1).

Lifestyle and Nutritional Measures

At first, given the documented associations between pro-inflammatory cytokines and lifestyle factors [54], appropriate lifestyle modifications, such as weight loss or exercise training [55], may be an important component in normalizing the dysregulated cytokine system activity in CKD [56]. Dietary interventions could also have an important role that has been, up to now, not enough explored. Because fish eaters have lower mortality on HD [57] and small studies in HD suggest that omega-3 fatty acids have a beneficial impact [58], the potential beneficial effects of fish oil or omega-3 fatty acids consumption merits further investigation in CKD patients. Of interest, a small randomized controlled trial with fish oil in HD patients found significant reductions in CRP concomitant with a rise in blood omega-3 levels [59]. Sex hormones may also be important for atheroprotection as men with low testosterone levels as well as women with low estrogen levels are at increased risk of CVD. The reported ability of sex hormones to interfere with cytokine production by repression of IL-6 mRNA may contribute to such protective effects [60]. This may have implications for natural sex-hormone derivatives like the flavonoid genistein present in soy. In fact, a study on isoflavone soy intervention in HD patients could show inverse correlations between changes in serum isoflavone levels and CRP levels [61]. Finally, a number of other nutritional interventions, such as fiber-rich food, nuts, probiotics, and diets low in advanced glycation end-products may have anti-inflammatory properties and should be evaluated in CKD patients [62, 63].

Unspecific Anti-Inflammatory Pharmacological Interventions

The role of unspecific anti-inflammatory pharmacological treatment strategies either alone or combined as a preventive therapy needs further evaluation. It is notable that several commonly used drugs may possess significant anti-inflammatory effects. Statins not only inhibit cholesterol synthesis but also showed anti-inflammatory actions [52, 64] and anti-oxidative properties [65] in HD patients. However, no effect on survival was demonstrated in the randomized controlled trial 4D [66]. In another study, IL-8, IL-6 and TNF- α level were reduced during aspirin consumption in HD patients [67]. ACE inhibitor (ACEI) treatment is associated with a reduction in IL-6 response to coronary artery graft surgery [68]. In accordance, we have found lower plasma levels of TNF- α , CRP [69] and adhesion molecules [70] in CKD patients treated by ACEI. Of interest, ACEI has also been shown to pre-

Table 1. Current status of anti-inflammatory treatment strategies in CKD patients

Current status as of 2008	
<i>I. Associated to dialysis treatment per se</i>	
Ultrapure dialysate	repeatedly shown to reduce CRP [90–93]
Biocompatible membranes	the inflammatory reaction is affected by choice of dialyzer [94]
Hemodiafiltration	on-line HDF does not provoke the inflammatory response [95]
Daily dialysis	dramatic positive effect on CRP in one study [96]
<i>II. Nutritional and lifestyle interventions</i>	
Physical training	resistance training reduced inflammation and improved nutritional status in CKD patients on a low-protein diet [55]
Omega-3 fatty acids	12-week fish oil supplementation decreases CRP in HD patients [59]
Soy	lower prevalence of inflammation and better outcome in Asian HD patients; soy supplementation decreases CRP in HD patients [61]
<i>III. Pharmacological interventions</i>	
Statins	no effect of atorvastatin on CRP in the 4D study [Wanner, pers. commun., 2007]
ACEI	reduction in IL-6 response to coronary artery graft surgery [68]; lower inflammatory [69] and adhesion molecules [70] in CKD patients treated by ACEI.
Sevelamer	a small randomized study showed decrease in CRP + increase in fetuin-A [75]
Gamma-tocopherol	small randomized trial in HD shows effect on IL-6 [83]
IL-1 antagonism	promising results in diabetic [88] and gout [89] patients
N-acetylcysteine	small study shows effect on outcome in HD [97]
Heparin	low-molecular-weight heparin reduces inflammation in HD patients [98]
Vitamin D	encouraging data on reducing inflammation biomarkers in other patient groups [72]

vent heart failure patients from wasting [71]. Other interesting approaches may include vitamin D, which effectively reduced the inflammatory milieu in a randomized controlled trial performed in chronic heart failure patients [72]. This is pertinent to CKD patients too, as vitamin D deficiency has been shown to be rather common and associated to increased short-term mortality [73]. Sevelamer has also been suggested to exert favorable changes in lipids and inflammatory markers with potentially useful antiatherogenic effects in HD patients [74]. In addition, short-term sevelamer intake significantly increased fetuin A levels and improved flow-mediated dilation in nondiabetic stage 4 CKD patients [75]. Both vitamin E and N-acetylcysteine, two natural antioxidants that may inhibit pro-inflammatory cytokine release [76, 77] and improve endothelial dysfunction [78, 79], have been shown to reduce cardiovascular events in rather small cohorts of dialysis patients [80, 81]. N-acetylcysteine is an especially interesting option to test considering its effect on reducing atheroma progression (probably via a decrease in oxidative stress) in an animal model of uremia-enhanced atherosclerosis [82]. Also, recent results from a randomized controlled trial with a combination of γ -tocopherol and docosahexaenoic acid (DHA) in HD patients showed a significant reduction in selected biomarkers of inflammation [83]. Finally, PPAR- γ activators such as rosiglitazone may be another interesting strategy to explore given their anti-inflammatory effects in a group of PD patients [84]. However, as the myocardial ischemic risk associated with rosiglitazone treatment

may be increased in type II diabetics patients [85], these drugs should be used with caution in dialysis patients.

Targeted Anticytokine Interventions

As targeted anticytokine treatment strategies have been shown to be effective in other patient groups with inflammation, these drugs may be of interest to study also in ESRD patients. Thalidomide, a drug with immunomodulatory, anti-inflammatory and antiangiogenic properties, exerts its therapeutic effects through the modulation of TNF- α . As thalidomide induces a Th2 response and has been associated with weight gain in other wasted patient groups, such as those with HIV or tuberculosis [86], it would be of interest to test the effects of this drug in ESRD patients. Pentoxifylline was recently shown to reduce TNF- α expression by >50% and to improve hemoglobin levels in HD patients with erythropoietin-resistant anemia [87]. Finally, results in type-2 diabetic patients [88] and in patients with acute gout [89] with interleukin-1-receptor antagonists have shown promising results.

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