

Chronic inflammation in end-stage renal disease and dialysis

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ABSTRACT

Under normal conditions, inflammation is a protective and physiological response to various harmful stimuli. However, in several chronic debilitating disorders, such as chronic kidney disease, inflammation becomes maladaptive, uncontrolled and persistent. Systemic persistent inflammation has, for almost 20 years, been recognized as a major contributor to the uraemic phenotype (such as cardiovascular disease, protein energy wasting, depression, osteoporosis and frailty), and a predictor of cardiovascular and total mortality. Since inflammation is mechanistically related to several ageing processes (inflammageing), it may be a major driver of a progeric phenotype in the uraemic milieu. Inflammation is likely the consequence of a multifactorial aetiology and interacts with a number of factors that emerge when uraemic toxins accumulate. Beside interventions aiming to decrease the production of inflammatory molecules in the uraemic milieu, novel strategies to increase the removal of large middle molecules, such as expanded haemodialysis, may be an opportunity to decrease the inflammatory allostatic load associated with retention of middle molecular weight uraemic toxins.

Keywords: chronic inflammation, end stage renal disease, expanded hemodialysis, middle molecules

INTRODUCTION

Chronic kidney disease (CKD) is an increasingly prevalent condition, recognized as a public health priority, affecting 10–12% of the population [1]. Thus, if CKD was a country, it would be the third most populous country on Earth. Apart from the economic burden that its treatment involves, achieving good long-term outcomes in this group of patients is a major challenge for the nephrology community. Patients with CKD are exposed not only to a higher comorbidity and poor quality of life, but also to an incredibly high overall mortality, mainly due to premature cardiovascular disease (CVD). Additionally, these patients experience higher rates of hospitalization, related also to the higher prevalence of, among others, nutritional, infectious, hormonal and psychological disorders.

Almost 20 years have passed since chronic inflammation first was recognized as a main component of the uraemic phenotype linked to CVD and protein energy wasting (PEW) [2], and a strong predictor of poor outcome in dialysis patients [3]. Although important steps have been taken in the understanding of the factors leading to chronic inflammation and the pathways involved in the pathophysiology of this common complication over the last 20 years, the knowledge available has not yet resulted in the development of solid therapeutic interventions for the treatment of this important component of the uraemic milieu. Within this brief narrative review on the underlying causes of chronic inflammation in end-stage renal disease (ESRD) and its implications for clinical outcomes, we focus on the significant role of large and especially middle molecules as the main pathologic factors contributing to inflammation, and discuss recent advances in dialysis techniques as a promising strategy to cope with this special situation.

Chronic inflammation: a maladaptive response that promotes premature ageing

Among the singular features exhibited by patients with CKD, chronic inflammation has one of the most prominent roles. A chronic inflammatory status is found in a great proportion of this population, with increasing prevalence accompanying the decline of renal function [4]. According to different studies, more than one-half of patients with CKD Stage 3, or higher stages, have increased levels of CRP [5, 6], with an even higher prevalence in patients in the final stages of the disease and in dialysis patients [7]. In this group of patients, systemic inflammation is associated with adverse outcomes including poor quality of life and increased mortality due to CVD and infectious complications, which in turn are linked to a state of acquired immune dysfunction, osteoporosis, depression, and metabolic and nutritional derangements leading to PEW [8]. Among a large number of inflammatory biomarkers, interleukin (IL)-6 seems to be the most robust predictor of comorbidity and outcome in CKD [9]. Emerging data support the notion that persistent inflammation as part of an increased allostatic load plays a major role in the prematurely aged phenotype that

develops when renal function declines [10], and in the progression of CKD [11].

The pathophysiology involved in the development of chronic inflammation in CKD has not yet been completely elucidated; however, it has been described as being the consequence of a multifactorial aetiology with interactions with a number of factors that emerge in the uraemic milieu. These include: (i) exogenous factors, such as dialysis membranes and central venous catheters; (ii) cellular factors, such as oxidative stress and cellular senescence; (iii) tissue factors, such as hypoxia, fluid overload and sodium overload; (iv) microbial factors, such as immune dysfunction and gut dysbiosis; and finally, (v) retention of uraemic toxins, such as indoxyl sulphate, advanced glycation end products and calciprotein particles. The described factors include not only the decline of glomerular filtration rate and the noxious effect of retained uraemic toxins, but they interact also with several complications usually present in this group of patients, such as comorbidities, superimposed acute illnesses, genetic predisposition and therapeutic interventions including the dialysis procedure *per se*. Among the different comorbidities, special attention should be paid to the contribution of the profound alterations of the gut microbial flora (called dysbiosis) typically found in CKD. The mutual interplay between the intestinal microbiota and the kidney has been acknowledged under the term ‘gut–kidney axis’ [12]. The high ammonia concentration responsible for lowering the pH in the gastrointestinal tract, the prolonged colonic transit, the dietary restrictions leading to decreased fibre intake, the fluid overload and medication (such as phosphate binders, proton pump inhibitors, potassium binders, oral iron and antibiotics) are only a few of the numerous factors that may underlie the altered composition of the intestinal microbiota in uraemic patients [13]. There are convincing findings in the literature linking systemic inflammation and gut dysbiosis in the uraemic milieu [14].

It is important to understand what leads to permanent activation of inflammation; a physiological process that, in the short term, is beneficial but when persistently activated promotes a series of complications. Indeed, the inflammatory process is a protective physiological mechanism in the host defence against infections, the tissue-repair response, adaptation to stress and restoration of a homeostatic state [15]. A controlled inflammatory response benefits the host with the eradication of the injurious stimuli and the initiation of the healing process in the tissue; but it can also become detrimental if deregulated. In fact, the pathological potential of inflammation is unprecedented for a physiological process, being associated with the burden of lifestyle and premature ageing [16]. It is notable that persistent inflammation (or ‘inflammageing’) is a common phenomenon in many chronic diseases related to ageing and the burden of lifestyle [17].

It has been proposed that in certain conditions—other than infection and tissue damage—inflammation might presumably act as an adaptive response to tissue malfunction or homeostatic imbalance in order to restore homeostasis. In this sense, an adaptive change often provides short-term benefits; however, in a chronic phase, it can become maladaptive, as

exemplified by a sustained decline in insulin sensitivity of the skeletal muscle, endothelial dysfunction or by squamous metaplasia of the respiratory epithelium, which may all be consequences of sustained inflammation. Indeed, inducible adaptive changes generally occur at the expense of many other physiological processes and therefore cannot be sustained without adverse side effects caused by the decline in the affected functions. In these circumstances, persistent inflammation is thought to contribute to an endless number of complications including arteriosclerosis, atherosclerosis, osteoporosis, frailty, PEW, diabetes, cancer and depression, to name a few, which seems to be very much the case of the chronic inflammatory status that accompanies CKD.

Uraemic retention solutes: the role of middle molecules

Along with the decrease of renal function, a large array of known individual uraemic retention solutes accumulate in patients with CKD. Their increased levels, which are frequently elevated several-fold, interact negatively with different biological functions, especially with the inflammatory, cardiovascular and fibrogenic systems, which at the same time are major actors in the high morbidity and mortality of CKD [18]. Classically, these uraemic retention solutes, also called uraemic toxins, have been classified based on their physico-chemical characteristics as small water-soluble compounds, protein-bound compounds and middle molecules [19].

Although all uraemic toxins have the capacity to affect the biological systems of the host, contributing to the phenotype of the uraemic syndrome, small water-soluble molecules are less of a problem considering that they are, in general, easily removed by dialysis due to their small size, especially if they are not protein-bound. On the other hand, the protein-bound uraemic toxins are a heterogeneous group of generally small solutes, which, due to their protein binding, are difficult to remove by dialysis. The group of toxins denoted middle molecules deserve special attention. This group is mainly composed of small proteins or peptides that can cross the glomerular filtration barrier under normal conditions (<58 kDa). Their minimum molecular weight has arbitrarily been set at 500 Da, although most middle molecules have a molecular weight of >10 kDa [20].

In contrast to the small water-soluble compounds and the protein-bound solutes, which to a large extent are intestinal metabolites of nutrition components, most of the middle molecules are generated endogenously. According to the most recent classification, middle molecules, which include cytokines and other pro-inflammatory mediators, constitute 23% of the number of identified uraemic toxins and uraemic retention solutes [21]. Although several molecules are included in this group (Table 1), the ones that are best characterized include cytokines, β_2 -microglobulin, ghrelin and parathyroid hormone. β_2 -microglobulin is considered as a prototypical middle molecule and is traditionally used as a marker of middle molecule removal. Both in pre-dialysis CKD and in dialysis patients [22], β_2 -microglobulin has been associated with several deleterious outcomes like pro-inflammatory processes [23], as well as with vascular stiffness [24], bone remodelling [25] or cognitive dysfunction [26]. Cytokines are another kind of middle molecule

Table 1. Examples of middle molecules considered as uraemic toxins

Middle molecules: uraemic toxins	
1.	Adiponectin
2.	Adrenomedullin
3.	Atrial natriuretic peptide (ANP)
4.	Basic fibroblast growth factor (BFGF)
5.	Calcitonin gene-related peptide (CGRP)
6.	Cholecystokinin
7.	Clara cell protein (CC16)
8.	Complement factor D
9.	Cystatin C
10.	Degranulation inhibiting protein I
11.	Delta sleep-inducing peptide
12.	Endothelin
13.	Guanylin
14.	Hyaluronic acid (hyaluronan)
15.	Interleukin-18
16.	Interleukin-1 β
17.	Interleukin-6
18.	Motiline
19.	Neuropeptide Y
20.	Parathyroid hormone
21.	Resistin
22.	Substance P
23.	Tumour necrosis factor
24.	Uroguanylin
25.	Vasoactive intestinal peptide (VIP)
26.	Vasopressin (ADH)
27.	β 2-microglobulin
28.	β -endorphin
29.	λ -Ig light chain

Information obtained from the database of the European Uremic Toxin Work Group.

that show increased circulating concentrations along with the decline of renal function. Indeed, CKD patients are characterized by an imbalance between pro- and anti-inflammatory cytokines [27], which has been associated with poor outcomes in CKD [28]. Apart from several factors described as being associated with increased production of these molecules, the problem increases because of the poor metabolic and renal clearance of these molecules, which is not compensated by the insufficient removal by the majority of current dialysis techniques, and thus increases the allostatic load and becomes a challenge in the treatment of this already frail population.

Possible therapeutic options addressing uraemic inflammation

Because inflammation in CKD has multiple causes, it is not likely that a single therapeutic strategy, i.e. a ‘silver bullet’, will ever be available. In our opinion, plausible treatment strategies should be considered from two different approaches: (i) interventions aiming to decrease the production of inflammatory molecules and (ii) strategies created to increase their removal by improved dialytic clearance (Figure 1).

Limit the production of inflammatory molecules. Because persistent inflammation may be a silent reflection of various undiagnosed pathological processes, it is essential that the levels of inflammatory markers are regularly monitored in an attempt to identify comorbid processes, such as infections, periodontal disease, autoimmune disorders, congestive heart failure and

neoplastic diagnoses [29]. Additionally, a healthy lifestyle with a balanced diet [30, 31], physical exercise [32] and non-smoking [33] should be highly recommended, considering the evidence of the beneficial effects of these kinds of interventions in terms of decreasing inflammation. Moreover, several drugs that are commonly used in the treatment of patients with CKD and other common pathologies have shown a potential favourable effect on inflammation. These drugs include statins [34], angiotensin-converting enzyme inhibitors [35–37], vitamin D [38] and sevelamer [39, 40], to name a few. Additionally, novel anti-inflammatory drugs have been created to target pro-inflammatory cytokines. Unfortunately, the data available about their efficacy in CKD patients are few and often not conclusive, and some of the benefits have just been extrapolated from results in the general population or other chronic patient groups. In this group of drugs, we can list thalidomide, pentoxifylline [41] and specific anti-inflammatory drugs, such as tocilizumab and canakinumab [42, 43]. These drugs have been used in other persistent inflammatory diseases, proving to be of value [31]. The recent report of a *post hoc* analysis of the BEACON trial showed that the Nrf2-agonist bardoxolone methyl preserves kidney function and delayed the onset of ESRD [44]. However, there is still a lack of data regarding the safety and concrete benefits of some of these medications in ESRD.

Increasing the clearance of inflammatory middle molecules by expanded haemodialysis.

In spite of promising results carried by the use of targeted anti-cytokine agents in inflammation of various origins in other chronic diseases, the evidence of their applicability in CKD is insufficient [45]. Taking into account the complexity of the uraemic milieu with many mutually related factors underlying the inflammatory response, it seems rather unlikely that targeting one element of this finely tuned orchestration of mediators could restore physiological balance. Therefore, strategies allowing for concomitantly approaching a wider range of mediators and targeting both increased generation and decreased clearance may be necessary. One emerging strategy is the concept of increasing the dialytic removal of higher molecular weight molecules. Whereas middle molecule clearance by conventional HD is poor, and therefore conventional low-flux HD has been unsuccessful in reducing the overall level of cytokines, novel dialysis strategies may represent the most efficient interventional options to decrease the concentrations of these molecules.

It is well known that improved clearance of bigger molecules would be achieved with the use of membranes with larger pores. However, high-flux dialysers, despite showing much better transport properties for the passage of middle molecules, are not effective in clearing solutes of molecular weight >15–20 kDa; i.e. the molecular weight range where most of the inflammatory mediators, such as IL-6, are found. Better removal can also be obtained by using large pore membranes with added convection by haemodiafiltration (HDF) or via longer dialysis sessions [46, 47]. In this regard, previous attempts to increase the pore size of the membrane have introduced additional problems related to the loss of beneficial molecules like albumin, due to a consequent reduction of the retaining selectivity of these membranes [48]. High cut-off membranes have a higher



FIGURE 1: Available therapeutic strategies for persistent inflammation in CKD. ACE, angiotensin-converting enzyme; HDx, Expanded hemodialysis; OI-HDF, On-line hemodiafiltration.

permeability for larger solutes than high-flux membranes, and therefore albumin losses in the dialysate can be substantial (9–23 g/treatment). However, repeated removal of albumin may not necessarily have any clinically meaningful deleterious effects on serum albumin levels. Indeed, the higher mortality associated with low serum albumin levels was recently shown to be dependent on the presence of inflammation in ESRD [49]. Thus, targeting inflammation may be one of the most important interventions to improve outcome in ESRD patients, not least in those with low serum albumin levels. This potential has been addressed by recent developments of dialysis membranes.

New membranes with a relatively high cut-off value have recently been introduced into clinical practice, with the potential to remove toxins in the high and middle molecular weight range that are increased in specific clinical condition like sepsis, rhabdomyolysis and haematological disorders [50]. In such circumstances, high molecular weight solutes—such as cytokines, myoglobin and free light chains—are the main targets for removal, and therefore so-called high retention onset (HRO) membranes have been developed. The main characteristic of these filters is a tight pore size distribution that results in a steep sieving curve, which allows an improved removal of uraemia retention molecules in the middle-to-high weight range, with marginal or no albumin leak. The use of HRO membranes in clinical dialysis has been named expanded haemodialysis (HDx), because they expand the known limits in membrane permeability and selectivity [50]. For this technique, a dialysis machine with ultrafiltration control is required. However, since no replacement solution or elevated ultrafiltration rates are

needed to perform the therapy, this implies a practical benefit over the currently used HDF techniques, where high volumes of replacement fluid are needed to achieve significantly different outcomes. Indeed, the first reports show comparable or even superior results of HDx compared with HDF, with a simpler treatment and less technical requirements [51, 52]. In two prospective, open-label, controlled, randomized, crossover pilot studies, 39 prevalent HD patients were studied in four dialysis treatments with medium cut-off (MCO) prototype dialysers and high-flux dialysers. In this study, the HRO membranes removed a wide range of middle molecules more effectively than high-flux HD, and even exceeded the performance of high-volume HDF for large solutes, particularly serum λ -free light chains [53]. In addition, treatment with an HRO membrane downregulated the expression of both IL-6 and tumour necrosis factor mRNA when compared with HF-HD. Thus, HRO membranes modulate inflammation in chronic HD patients compared with high-flux dialysers. Transcription of pro-inflammatory cytokines in peripheral leukocytes is markedly reduced and removal of soluble mediators is enhanced after 12 weeks of expanded HDx with no significant adverse events [54]. On the other hand, in a recent retrospective analysis of 10 patients treated first with online HDF who were thereafter switched to MCO HD over a 1-year period, the authors did not find any significant difference in the removal of urea, creatinine, β 2-microglobulin and myoglobin, in the values of nutritional markers as either albumin or pre-albumin [55].

Taken together, some recent studies bring hope regarding the beneficial effect of HDx as an opportunity to

decrease the inflammatory allostatic load associated with retention of middle molecular weight uraemic toxins, including several inflammatory mediators. However, more data are needed in order to confirm the potential beneficial effect of this therapy on quality of life, number of hospital admissions, infectious and cardiovascular complications, and, in future studies, improvement of patient survival, with a special emphasis on defining the group of patients that would benefit the most from such a therapy.

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CONFLICT OF INTEREST STATEMENT

B.L. is employed by Baxter Healthcare Corporation. P.S. has served on Baxter Healthcare Corporation advisory boards and lectured in symposia sponsored by Baxter Healthcare Corporation.

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