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Immune Mechanisms Involved in Cardiovascular Complications of Chronic Kidney Disease

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Key Words

Chronic kidney disease, inflammation · Cardiovascular disease · Myocardiopathy · Atherosclerosis

Abstract

A sustained status of chronic inflammation is closely linked to several complications of chronic kidney disease (CKD), such as vascular degeneration, myocardial fibrosis, loss of appetite, insulin resistance, increased muscle catabolism and anemia. These consequences of a chronically activated immune system impact on the acceleration of atherosclerosis, vascular calcification and development of heart dysfunction. Recent evidence suggests that these immune-mediated consequences of uremic toxicity are not only important to stratify the risk and understand the mechanisms of disease, but also represent an important area for intervention. Thus, the aim of this brief review is to discuss the immune mechanisms behind atherosclerosis and myocardiopathy in CKD. We also display the emerging evidence that strategies focusing on modulating the immune response or reducing the generation of triggers of inflammation may represent an important tool to reduce mortality in this group of patients. Ongoing studies may generate the evidence that will translate these strategies to definitive changes in clinical practice.

Introduction

Signs of an activated immune system and elevated levels of inflammatory mediators can be observed in the early stages of chronic kidney disease (CKD) and increase with the progression of renal dysfunction. This chronic inflammatory state is closely linked to several complications of CKD, such as vascular degeneration, myocardial fibrosis, loss of appetite, insulin resistance, increased muscle catabolism and anemia. Potentially, these consequences of a chronically activated immune system impact on the acceleration of atherosclerosis, vascular calcification and development of heart dysfunction. Not surprisingly, the presence of systemic inflammation is an important predictor of poor outcome in CKD patients, and the central role of immune-mediated changes in the heart and vascular system (the main cause of mortality in CKD) has been consistently described [1]. Recent evidence suggests that these immune-mediated consequences of uremic toxicity are not only important to stratify the risk and understand the mechanisms of disease, but also represent an important area for intervention. Thus, the aim of this brief review is to discuss the immune mechanisms behind atherosclerosis and myocardiopathy in CKD. We also display the emerging evidence that shows that strategies focusing on modulating the immune re-

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sponse or reducing the generation of triggers of inflammation may represent an important tool to reduce mortality in this group of patients.

Immune Mechanisms Involved in the Development of Cardiovascular Disease in CKD

The interaction between kidney failure and the cardiovascular system, currently defined as cardiorenal syndrome, appears to be largely mediated by the immune system, which recognizes the uremic state as a continuous aggression to cells and tissues. The uremic toxins consist of heterogeneous substances, including organic compounds and peptides, with proinflammatory effects [2]. Uremic toxin accumulation, which is only partially corrected by dialysis, as well as dialysis-related factors, such as interactions between blood and dialyzer, endotoxin presence in water, access-related infections, peritoneal dialysis solutions with high glucose concentration, low pH and the presence of glucose degradation products, represent the chronic stimuli to the inflammatory response [3]. In concert these responses to multifactorial stimulation impact on the mechanisms involved in the uremic vascular degeneration and myocardiopathy, which will be reviewed in the following section.

Inflammatory Mechanisms Involved in the Vascular Changes in CKD

Vascular changes that characterize the atherosclerotic process are initiated and perpetuated by the interaction of immune cells with cells of the vessel wall. Leukocyte interactions with vascular endothelium during inflammation occur through steps involving selectin-mediated leukocyte rolling, mild adhesion mediated by adhesion molecules (vascular adhesion molecule 1 and intercellular adhesion molecule-1) and subsequent firm adhesion mediated by chemokines (particularly the monocyte chemoattractant protein 1) and interleukin-8 [4]. There is increasing evidence generated from experimental and clinical studies that these early stages of atherosclerosis are extremely important [5]. Vascular inflammatory responses, through chemotactic and haptotactic pathways, not only contribute to the growth and expansion of early lesions, but also participate in plaque destabilization, resulting in thrombotic complications associated with significant morbidity and mortality [6]. Interestingly, animal models that combine atherosclerosis-prone mice with renal dysfunction result not only in increased plaque formation, but show also increased signs of vascular inflammation, oxidative stress and calcification [7].

The endothelium is a continuous layer of cells that separates blood from the vessel wall, and, as an active and dynamic tissue, it controls many important functions, including maintenance of blood circulation and fluidity as well as regulation of vascular tone, coagulation and inflammatory responses [8]. The constant aggression of the endothelium by uremic toxins leads to modification in the endothelial cell phenotype and to endothelial dysfunction, with secretion of many proinflammatory molecules, such as tumor necrosis factor (TNF) α and C-reactive protein [9–12]. Endothelial cell dysfunction can be evaluated by measuring indices such as flow-mediated vasodilation and indirectly by measuring circulating markers of endothelial cell dysfunction such as monocyte chemoattractant protein 1, vascular adhesion molecule 1 and intercellular adhesion molecule 1 [13] and markers of processes that are known to interfere with endothelial cell function, e.g. oxidative stress, microinflammation, adipokine abnormalities such as low serum adiponectin levels, vascular calcification and others [14]. Finally, prospective data strongly suggest that endothelial activation and vascular inflammation occur early in the atherosclerotic process and predict cardiovascular events in the general [15] and CKD [16] populations. Anti-inflammatory strategies to reduce vascular inflammation will be reviewed later in this article.

Inflammation and Myocardiopathy

Left ventricular hypertrophy (LVH) is the most frequent cardiac alteration in end-stage renal disease (ESRD) patients, documented in 75–80% of patients undergoing dialysis therapy, and is an independent risk factor for survival [17]. The pathogenic factors involved in the generation of LVH in CKD and ESRD patients are diverse and complex, involving afterload-related factors (elevated systolic and diastolic arterial hypertension), preload-related factors (expansion of intravascular volume, anemia) and non-afterload- or preload-related factors [18, 19]. The links between these triggers and myocardial changes are largely mediated by the immune system.

LVH is characterized not only by an increased myocardial fiber mass, but also by interstitial fibrosis [20], and many abnormalities such as cardiomyocyte hypertrophy, myocardial fibrosis and thickening of intramural arteries and arterioles are constant findings in heart biopsies and necropsy studies in CKD patients with LVH [21]. Processes seemingly unrelated to both afterload or preload, such as activation of the mammalian target of

rapamycin pathway and those related to the parathyroid hormone-vitamin D-phosphate axis, microinflammation and oxidative stress, are also emerging as important in the production of LVH and cardiac fibrosis in patients with CKD and ESRD [19]. Activation of the intracardiac renin-angiotensin system appears to be critically involved in this pathway, and both angiotensin II and aldosterone can also be involved in myocardial cell hypertrophy and fibrosis independent of afterload [22]. These phenomena can lead to a progressive impairment in contractility and a stiffening of the myocardial wall, leading to systolic and diastolic dysfunction and ultimately to dilated cardiomyopathy and diastolic and/or systolic congestive heart failure [23].

These nonhemodynamic/volume-related factors represent potential new targets for treatment directed at modifying LVH and its clinical consequences. The cardiovascular system is one of the most important targets of the inflammatory activation, so cardiovascular risk stratification is desirable in the clinical management of CKD patients, and biomarkers such as inflammatory cytokines are increasingly used in these patients.

Inflammatory cytokines may play an important role in the pathogenesis of myocardial damage in CKD patients, determining a depressant effect on the myocardium and inducing ventricular dysfunction [24]. Circulating levels of TNF-α and interleukin 6 are increased in patients with heart failure and may promote apoptosis [25]. Additionally, TNF-α may induce acute cardiac dysfunction mediated by nitric oxide, and, moreover, the observation that failing hearts express elevated levels of TNF-α suggests that overexpression of this cytokine may be one of several different maladaptive mechanisms responsible for the progressive cardiac decompensation that occurs in advanced heart failure [26]. There is clinical evidence revealing an excess of cytokines such as cardiotrophin 1 and transforming growth factor β_1 in CKD. Mechanical overload imposed on the myocardium is the initial stimulation to production of transforming growth factor β_1, which may further increase the response to anemia-related myocardial hypoxia [27].

Patients with fluid overload, such as patients with congestive heart failure, present signs of systemic inflammation that reduce when the disease is compensated [28]. This inflammatory state appears to be associated with an altered gut barrier permeability that occurs as a consequence of the edema, allowing the translocation of macromolecules including endotoxins into the circulation, such as lipopolysaccharides [29]. As a consequence of the presence of circulating endotoxins, the immune system may be activated, generating a chronic inflammatory status, potentially working as a drive to cardiovascular disease [30].

CKD and ESRD patients have a high prevalence of vitamin D deficiency [31] that is characterized by low levels of 25-hydroxyvitamin D and frequently low levels of 1,25-dihydroxyvitamin D, the hormonal form of this vitamin, and there is significant evidence suggesting beneficial cardiovascular effects of vitamin D therapy in uremia [32]. Recent findings from several large observational studies [33] have suggested that the benefits of vitamin D receptor activators may extend beyond the traditional parathyroid hormone-lowering effect and could result in direct cardiovascular and metabolic benefits. Vitamin D may play a role in the inflammatory response, modulating production of cytokines involved in calcification and atheroma formation [34], upregulating anti-inflammatory molecules and, also, modulating the expression of tissue matrix metalloproteinases. Indeed, vitamin D can act as a negative endocrine regulator of renin-angiotensin synthesis [4] and reduces cardiac hypertrophy, all processes that may be directly related to cardiovascular disease in CKD. Additionally, vitamin D seems to play a crucial role in the organization of cardiac tissue, regulating intracellular calcium levels, maturation, differentiation and proliferation of cardiac cells [35].

Inflammation-Focused Targets for Intervention Aiming to Reduce Cardiovascular Mortality in CKD

There are two potential therapeutic approaches using inflammation as a target that may result in cardiovascular benefits in CKD patients: pharmacological manipulation of cell response and reduction of source of ligands. There is an increasing number of studies analyzing the potential impact of these strategies, which will be reviewed in the following section.

Pharmacological Manipulation of Cell Response

Although pharmacological interventions in dialysis patients frequently result in negative findings [36, 37], some randomized and controlled (or not) clinical trials with cardiovascular endpoints reveal interesting aspects in the area of inflammation. First, two classes of the renin-angiotensin system (angiotensin-converting enzyme inhibitor and angiotensin II receptor blockers, antihypertensive agents with proven anti-inflammatory activity) have been tested in clinical trials on a dialysis population [38, 39]. The results of a randomized trial using fo-

sinopril [38] showed a slight benefit for this agent in comparison to placebo. In another randomized trial with a small number of patients [39], candesartan significantly reduced cardiovascular events and mortality in patients on chronic maintenance hemodialysis. More recently, Suzuki et al. [40] verified that treatment with an angiotensin receptor blocker was independently associated with reduced fatal and nonfatal cardiovascular disease events in a hemodialysis population, although the large effect may be a spurious finding because of the small sample size of that trial.

In observational studies, statin (another drug with anti-inflammatory effects) users had lower mortality than non-statin-using hemodialysis patients [41], results that were not confirmed by randomized controlled trials in ESRD hemodialysis patients [36, 42], even with substantial reductions in low-density lipoprotein. Although the treatment with rosuvastatin had no significant effect on the composite primary endpoint of death from cardiovascular causes, nonfatal myocardial infarction or nonfatal stroke [42], there was a reduction in mean high-sensitivity C-reactive protein, an important inflammatory biomarker in CKD patients. In the AURORA trial [42], it was noticeable that inflammation at the baseline was one of the most important risk factors for mortality when the population was treated as a cohort, which points to the need of trials looking at the effect of statins in a select group of patients with inflammation.

Renal dysfunction is frequently associated with oxidative stress, which may be an interesting target for therapeutic interventions. In this field, some clinical trials emerged with positive results. One of them investigated the effect of high-dose vitamin E supplementation on cardiovascular disease outcomes in hemodialysis patients with preexisting cardiovascular disease. After a median follow-up of 519 days, the use of vitamin E was associated with reduced cardiovascular disease endpoints and myocardial infarction [43]. Another antioxidant agent, acetylcysteine, a thiol-containing antioxidant, had its effects observed in a randomized controlled trial in hemodialysis patients. Fatal and nonfatal cardiovascular endpoints, as well as mortality were attenuated by acetylcysteine use [44].

The circulating levels of 25-hydroxyvitamin D_3 and 1,25-dihydroxyvitamin D_3 can potentially influence the activity of many tissues and cells that have a vitamin D receptor and have no function in regulating calcium homeostasis and bone health. These include, among others, the cardiomyocytes, active T and B lymphocytes, mononuclear and endothelial cells [45]. As discussed, dialysis patients on different types of activated vitamin D and analogs [33] have a survival advantage, probably related to the systemic activation of vitamin D receptors, acting as a negative endocrine regulator of renin-angiotensin synthesis [4] and inflammation and reducing cardiac hypertrophy [32].

LVH in CKD and ESRD is frequently related to myocardial fibrosis, by mechanisms that are not directly related to hypertension or fluid overload. A potential and promising target for intervention in this situation is the mammalian target of rapamycin pathway, overexpression of which may be related to myocardial fibrosis in such patients. In experimental models [19], cardiac hypertrophy in uremic mice was reduced by rapamycin use and not by reduction of blood pressure, suggesting that uremic cardiomyopathy is mediated, at least partially, by activation of a pathway that involves the mammalian target of rapamycin pathway.

Reduction of Source of Ligands

Immune aspects related to membrane biocompatibility in dialysis patients are frequently the object of clinical research. In hemodialysis patients, the use of high-flux hemodialysis membranes was associated with better survival, specifically in the subgroup of patients with systemic inflammation or malnutrition (seric albumin ≤ 4.0 g/dl), and in diabetic patients. In peritoneal dialysis, the bioincompatibility of peritoneal dialysis fluids has been attributed to low pH, lactate, glucose, glucose degradation products and osmolality. In a retrospective observational study in peritoneal dialysis patients [46], the treatment with a novel biocompatible peritoneal dialysis fluid with low glucose degradation product concentration and neutral pH confers a significant survival advantage, even after adjustment for age, gender and diabetes status. The exact mechanisms for such a survival advantage could not be determined, but reduction of inflammation may be an important factor.

Periodontal disease is associated with cardiovascular disease, may work as an occult source of chronic inflammation and is thought to accelerate systemic atherosclerosis. In a recent clinical study in hemodialysis, patients with moderate-to-severe disease compared to those with mild or no periodontal disease had a significant association with death from cardiovascular causes. Intervention trials to determine if treating periodontitis (and other hidden infections) reduces cardiovascular disease mortality in dialysis patients are desirable.

Endotoxemia has recently been related to fluid overload and systemic inflammation in CKD nondialysis [30]

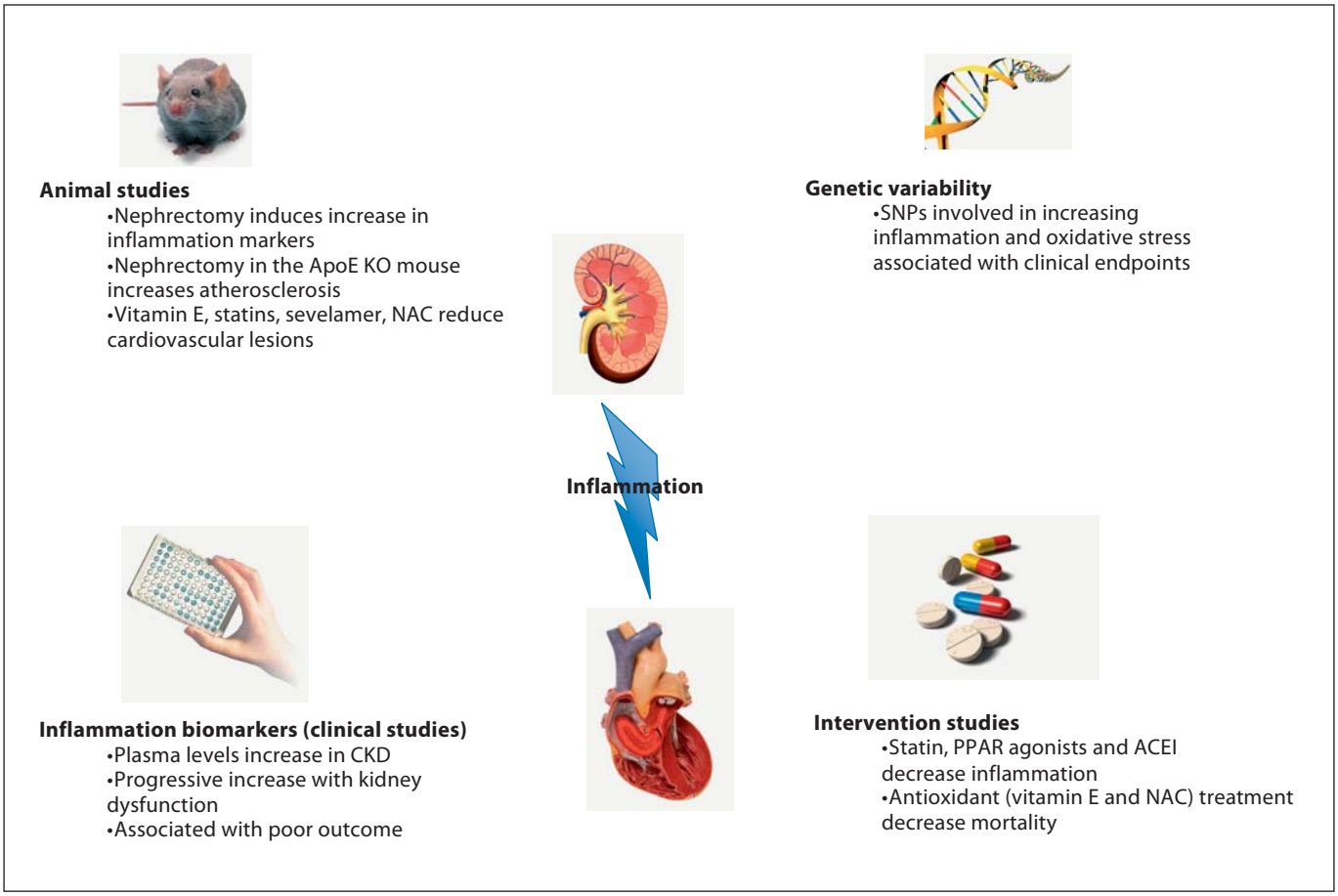

Fig. 1. Immune mechanisms involved in the interaction between kidney dysfunction and cardiovascular complications analyzed using different investigation strategies. ApoE = Apolipoprotein E; NAC = N-acetylcysteine; SNPs = single-nucleotide polymorphisms; PPAR = peroxisome proliferator-activated receptor; ACEI = angiotensin-converting enzyme inhibitor.

and in peritoneal dialysis patients [47]. Although the drug had been created to be used as a phosphate binder, recently sevelamer hydrochloride showed a potential endotoxin-binding effect in the intestinal lumen, reducing systemic inflammation in an experimental model [48]. Other potential pleiotropic effects of sevelamer that could have cardiovascular impact include a lipid-lowering action and reduction in C-reactive protein levels [49]. Recently, Stinghen et al. [50] demonstrated in a clinical study that sevelamer treatment leads to a decrease in C-reactive protein levels, which was accompanied by a parallel decrease in endotoxemia, suggesting that endotoxemia may contribute to the systemic inflammation in hemodialysis patients, which was partially reduced by the use of sevelamer.

Conclusions

In summary, there is strong evidence derived from animal models, cellular and molecular studies linking inflammation to cardiovascular alterations in CKD (fig. 1). Also, several inflammation biomarkers are related to disease state, degree of kidney dysfunction and prediction of cardiovascular events and mortality. Emerging evidence is showing that the reduction of mortality in CKD patients can be achieved with anti-inflammatory strategies. Ongoing studies may generate the evidence that will translate these strategies to definitive changes in clinical practice.

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