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REVIEW

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# Chronic kidney disease and inflammation in pediatric patients: from bench to playground

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**Abstract** Signs of an activated immune system can be observed already in the early stages of chronic kidney disease (CKD). Markers of a chronically activated immune system are closely linked to several complications of CKD, such as accelerated atherosclerosis, vascular calcification, insulin resistance, increased muscle catabolism, loss of appetite, bone remodeling, and increased peritoneal permeability. Interestingly, all the aforementioned pathological states resemble a state of accelerated ageing and are strongly associated with increased morbidity and mortality in CKD patients. In recent studies, signs of inflammation have been shown as predictors for mortality in dialysis patients, and the role of inflammation as a risk factor for complications of CKD in children has emerged. Although preliminary findings suggest that inflammation is highly prevalent in the pediatric population with CKD, information related pathogenic links and to clinical outcomes is lacking. For the future, it is crucial for investigations to address the mechanisms and complications of inflammation that are manifested in pediatric patients with CKD in all stages. Since early identification and intervention may generate the most efficient strategies for prevention and treatment of cardiovascular disease in CKD patients, the pediatric population deserves special attention in future studies. In this review, we discuss the mechanisms involved in the inflammatory activation and the main causes and consequences of the inflammatory state observed in the CKD patient, with special emphasis on the pediatric population.

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## Introduction

Inflammation is the body's reaction to invasion by an infectious agent, antigen challenge, physical, chemical or traumatic damage. This reaction must be precisely regulated because both deficiencies and excesses in an inflammatory response may lead to morbidity and mortality [1]. Indeed, recent evidence has linked the same immunological defense mechanism called inflammation to a high risk of developing pathological states such as insulin resistance, wasting disorders, and atherosclerotic disease. In the adult population signs of an activated immune system are observed in the early stages (as early as in stage 3) of chronic kidney disease (CKD) [2]. Markers of a chronically activated immune system are closely linked to several complications of CKD, including accelerated atherosclerosis, vascular calcification, insulin resistance, increased muscle catabolism, loss of appetite and renal osteodystrophy [3]. Interestingly, all the aforementioned pathological states are strongly associated not only with increased morbidity and mortality in CKD, but also with the accelerated ageing process (Fig. 1). Indeed, in recent studies performed in the adult population, inflammation is a powerful predictor of mortality in dialysis patients [4].

Although most of the studies published on the area of immune dysfunction in CKD, the fact that these patients also demonstrate clear clinical features of ineffective immune response deserves consideration. This is clearly exemplified by the low rate of successful immunization, low response in tuberculin tests, decreased rejection rate in uremic patients, and particularly the high rate of infection complications (and mortality) observed in uremic patients [5, 6, 7]. The net consequences of the uremic immune disorder (profound immunodeficiency with a state of cellular activation) urge further attention.

About 30–50% of adult CKD patients [8] have serologic evidence of an activated inflammatory response in

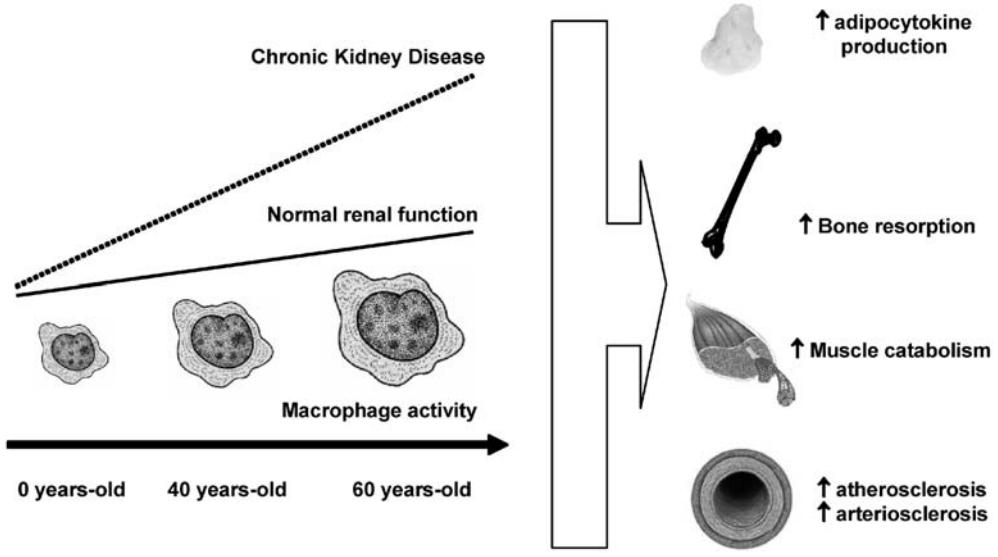


**Fig. 1** Schematic representation of the concept of the accelerated ageing process induced by chronic kidney disease. Renal dysfunction through several mechanisms described in the text activates inflammatory cells to generate a chronic and increasing inflammatory reaction (mainly due to a hyperactive macrophage), which mimics and amplifies the immune ageing process. Consequently, clinical features of the elderly (increased adipocytokine production, bone remodeling, muscle catabolism, and vascular changes) are observed earlier in patients with chronic kidney disease

stage 5 of CKD, even before the initiation of renal replacement therapy [9]. Such signs of a sustained low-grade inflammation are also commonly observed (and perhaps enhanced) following the initiation of either hemodialysis (HD) [10] or peritoneal dialysis (PD) [11] therapy, despite the clinical stability of the patient. Such findings are equally strong predictors of mortality in both groups of dialysis patients [12].

The most common non-traditional marker of inflammation in the clinical practice has been an elevated serum concentration of C-reactive protein (CRP). According to the American Heart Association [13], patients with CRP levels lower than 1 mg/l have low risk for developing cardiac disease, those with CRP between 1 and 3 mg/l have an intermediate risk, and those with CRP between 3 and 10 are at a high risk.

In children, information is lacking in regard to the prevalence of chronic inflammation and its association to clinical outcome. Preliminary data from our group (unpublished observation) show that approximately 40% of pediatric CKD patients (including predialysis and dialysis patients) demonstrate CRP levels above 1 mg/l (mean 4 mg/l), which is considered an intermediate risk factor for CVD in adults. Moreover, 17% of our patients presented CRP levels higher than 3 mg/l, which is compatible with a high risk of CVD. In general, the prevalence of low grade inflammation in the pediatric CKD population appears to be much higher than in the general pediatric population, even when infantile obesity is considered [14].

Although complications of CKD affect populations independent of age, studying the pediatric CKD population is still challenging. There are few well-designed studies in this area, and these studies usually include a limited number of patients [15]. Most available data derive from registries such as the United States Renal Data System (USRDS) [15], the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) [16], and the European Renal Association-European Dialysis and Transplant Association Registry (ERA-EDTA) [17]. Although registry data are extremely important, they are not population-based in nature and therefore of limited value. Thus, there is an urgent need for multicenter cooperative studies that can contribute to the understanding of long-term complications seen in CKD that could be better managed if diagnosed early or predicted in children [3]. In CKD, patients often demonstrate dialysis-related complications, such as dialysis solution or dialyzer bioincompatibility and quality of dialysis water and dialysis-unrelated factors, such as uremic toxicity, comorbidities, and chronic infections that may contribute to a state of chronic inflammation [3]. The aim of this review is to discuss the mechanisms of inflammatory activation and the main causes and consequences of the inflammatory state observed in the CKD patient, with a special emphasis on the pediatric population.

## Mechanisms of systemic inflammatory activation in CKD

As a consequence of tissue damage, the innate and, later, the adaptive immune systems are triggered, as part of a complex reaction of the body expressing the response to damage of its cells. This complex response is the basis of what is currently described as inflammation. Thus, inflammation can be considered a two-edged sword, since it has a pivotal role in fighting invasion by an infectious agent or antigen challenge, but also lead to further tissue

**Table 1** Potential causes of chronic inflammatory activation in children with chronic kidney disease

| Chronic kidney disease (particularly after stage 3) |
|---|
| Unrecognized persistent infections (periodontal disease, tuberculosis, *Helicobacter pylori* , *Chlamydia pneumoniae*) |
| Introduction of bacteria with chronic urinary tract infections in uropathy-related renal disease |
| Uremic toxin accumulation |
| Fluid overload |
| Reduced renal clearance and increased expression of pro-inflammatory cytokines |
| Calcium phosphorus disturbances and hyperparathyrodism |
| Co-morbidity (chronic heart failure, diabetes mellitus, obesity, hypertension, physical inactivity, dyslipidemia) |
| Additional causes in HD |
| Tunneled central lines, graft and arterio-venous fistula infections |
| Complement activation due to blood dialyzer contact |
| Exposure to endotoxins and other cytokine-inducing substances from dialysate |
| Additional causes in PD |
| Peritonitis and exit site infection |
| High glucose, acidic pH, high osmolarity of the dialysate |
| Glucose degradation products and advanced glycation end-product absorption from dialysate |

damage when uncontrolled. The development of inflammatory reactions is controlled by cytokines (such as IL-1, IL-6, TNF-$\alpha$, and TGF-$\beta$), by products of the plasma enzyme systems (such as complement, the coagulation clothing, kinin and fibrinolytic pathways), by prostaglandins and leukotrienes, and by vasoactive mediators (histamine and serotonin).

Cytokines interact first with high-affinity cell membrane receptors and then regulate the transcription of a number of cellular genes, which results in changes in cell behavior. As a consequence of the initial activation, cytokines transform their information signal on target cells, which can be localized in any body compartment (i.e., vascular tissue, muscle, brain, and liver), leading to well-known complications of CKD (Fig. 1). In this scenario, the high prevalence of chronic infections, the accumulation of uremic toxins and fluid overload, the interaction between blood and a dialyzer, and the introduction of exogenous components (such as endotoxins from the dialysate), all of which are commonly observed in stage 5 CKD, represent an interesting model of chronic stimuli to the inflammatory response [3].

## Causes of chronic inflammation in CKD

The causes of a chronic pro-inflammatory state in CKD patients are not well understood, although it is likely that the causes are multifactorial (Table 1) and depend on the definition of inflammation. First, chronic inflammation can be defined as an increase in plasma levels of pro-inflammatory cytokines, caused by both decreased renal clearance and increased cytokine production. When serum levels of interleukin (IL)-1 and tumor necrosis factor (TNF)-$\alpha$ were compared in 29 adult patients prior to the initiation of dialysis versus those on long-term therapy (13 on PD and 42 on HD) and 15 healthy controls, no differences were found; however, patients with renal disease had higher levels of these cytokines no matter the CKD stage [18]. Since this was a cross-sectional study with a single measurement, it must be emphasized that the study design may have contributed to the lack of significant difference in cytokine concentrations, since both IL-6 and TNF-$\alpha$ have large standard deviations. On the other hand, the deterioration of renal function has been associated with a significant increase in serum cytokine levels in CKD patients, and creatinine clearance correlates with the circulating levels of various cytokines and their soluble receptors in patients with varying degrees of renal failure [9, 19]. Moreover, lower urinary IL-6R excretion is found in CKD patients compared to controls [20], and reduced renal function may affect both TNF-$\alpha$ [21] and IL-1 [22] clearance in nephrectomized rats.

An elevated serum concentration of CRP is one of the most common non-traditional markers used to stratify cardiovascular risk, and it has been used to identify patients with chronic inflammation, since it reflects a pro-inflammatory state. Most published studies show consistent findings of a strong correlation between circulating CRP and pro-inflammatory cytokines, particularly IL-6, which is dependent on TNF and IL-1 stimulation. Therefore, CRP reflects the hepatic response to high circulating pro-inflammatory cytokine levels, and the same causes described above could be responsible for high CRP levels in CKD patients. Other non-dialysis-related causes of elevated CRP in CKD patients might include factors such as chronic heart failure with fluid overload [23], which appears to be exacerbated with the progression of renal disease [24].

Another important factor for the activation of the inflammatory response is the immunological effect of uremic toxins on the immune system. Examples of uremic toxins with pro-inflammatory effects are the advanced glycation end products (AGEs). When aldehyde or ketone groups of carbohydrates react with amino acids, a variety of AGEs are formed. In CKD patients, it is possible that an accumulation of AGEs caused by decreased renal clearance or the increased oxidative stress might also promote inflammation. In fact, a correlation has been found between pentosidine, a type of AGE, and CRP in patients with stage 5 CKD [25]. In addition, a recent in vitro study [26] showed that AGEs can trigger an inflammatory response in monocytes through the cell receptor for AGEs (RAGE), leading to the activation of NF$\kappa$-B. Similar to what is observed in adults, children with diabetes and CKD also present high circulating levels of AGEs, which are only partially corrected after transplantation, probably because some patients remain with impaired renal function, but also because the reduction of tissue AGEs seems to require several years [27, 28]. Similar to AGEs, several other uremic toxins may be involved in the inflammatory activation in CKD, but further studies need to confirm that hypothesis.

Alterations in body composition have emerged as another determinant of inflammation. It has been increas-

ingly evident that fat tissue is not only an inert energy storage depot, but also an active endocrine organ that produces several adipokines, including leptin, resistin, adiponectin, IL-6, and TNF-$\alpha$ [29]. Recently, we have found a relationship between body fat mass (particularly truncal fat mass) and inflammatory parameters in CKD patients close to the start of dialysis [30]. Thus, it is likely that fat tissue production of inflammatory markers may contribute to inflammation in CKD patients. In children with normal renal function, being overweight is associated with higher CRP concentrations and higher white blood cell counts [31].

Although circulating levels of pro-inflammatory cytokines are known to be elevated even before the initiation of dialysis therapy, it is clear that the dialysis procedure per se may cause additional inflammatory activity. Signs of inflammation are commonly observed in both HD [10, 32] and PD [33, 34] patients, and it seems that HD and PD have similar effects on systemic inflammation. However, several lines of evidence suggest that also factors associated with the dialysis procedure might contribute to an inflammatory response (Table 1). Initially, Haubitz et al. [35] demonstrated that acute-phase proteins are induced during HD, probably due to cytokine release as a consequence of the blood-dialyzer contact. Schindler et al. [36] suggest that the dialyzer membrane may play a role in the induction of an inflammatory reaction during the dialysis procedure. Moreover, data by Memoli et al. [20] suggest an important role of poor dialysis bioincompatibility of cuprophane on enhancing the inflammatory effects of IL-6. Furthermore, the quality of water used to prepare the dialysate [37] might contribute to inflammation. Nevertheless, the extent to which bacterial products from contaminated dialysate enter a patient's blood depends upon the type (cellulosic vs. synthetic) and permeability (low flux vs. high flux with backfiltration) of the hemodialysis membrane in use [38]. In certain circumstances, cytokine-inducing substances may penetrate intact dialyzer membranes and contribute to chronic inflammation associated with long-term HD therapy. As an example, bacterial fragments generated by biofilms are able to cross the dialysis membrane and stimulate an inflammatory response in the patient [39]. Recently, Goldstein et al. [40] observed that the chronic inflammatory state of pediatric HD patients was not related to the hemodialysis treatment, but rather to the dialysis duration and adequacy, suggesting that either more frequent dialysis or enhanced cytokine clearance may ameliorate the chronic inflammatory state observed in this group of patients [40].

In PD patients, the prolonged exposure to conventional bioincompatible glucose-based solutions [high osmolarity, glucose, and lactate concentrations, a low pH, and high content of glucose degradation products (GDPs)] can be a risk factor for inflammatory activation. Glucose as such and perhaps GDPs could contribute to the reported positive correlation between dialysate IL-6 and the concentration of glucose in the dialysis fluid [41]. Accordingly, we have recently reported that a high peritoneal solute transport rate (PSTR) is associated with higher levels of both intraperitoneal and systemic IL-6 [42]. Since high PSTR [42] and volume overload [43] are both associated with inflammation, one may hypothesize that prolonged use of a high glucose PD solution indirectly increases the risk of both systemic and local inflammation in PD patients. Furthermore, it is possible that GDPs can be absorbed from the peritoneal cavity into the circulation [44], leading to the accumulation of plasma AGEs, a situation that could increase cardiovascular harm caused by these compounds. Taking together, it seems likely that the bioincompatibility of PD solutions (in particular the high levels of glucose and GDPs) are modifiable factors contributing to inflammation among PD patients.

## Consequences of inflammation in CKD

The importance of inflammation in clinical practice is based on the strong associations between circulating markers of inflammation and pathological states such as metabolic disturbances, wasting disorders, and, above all, atherosclerotic disease. These findings are very consistent in several disease groups, including CKD patients [9]. The annual mortality rate due to CVD in stage 5 CKD patients over 25 years of age (in which the prevalence of inflammation is very high) is approximately 9%, 10–20 fold higher than that of the general population, even when adjusted for age, gender, race, and the presence of diabetes mellitus [45]. Although several links between factors leading to high mortality and inflammation could be discussed, we will concentrate on atherosclerotic CVD and malnutrition.

Initially, CVD is the cause of death in nearly 50% of adult dialysis patients. This high mortality rate suggests that CKD patients suffer from accelerated atherogenesis [3], leading to peripheral, cerebral, and cardiac ischemic disease. The risk of death is strikingly higher especially in the younger patients with CKD [45], suggesting that the atherogenic process starts early in life. As an example, CKD patients from 25 to 34 years of age have a 100–120-fold higher mortality than the general population [46, 47]. In accordance, children with CKD have an increased risk for death compared with the general pediatric population, mainly due to cardiovascular causes. In fact, an observational study analyzing a large number of patients who started dialysis as children and died before 30 years of age showed that cardiovascular deaths accounted for 23% of the overall mortality [48]. The causes of cardiovascular mortality in this study included sudden death, myocardial infarction, cardiomyopathy, arrhythmias, and other cardiac causes. The authors concluded that further studies are needed to identify risk factors associated with cardiovascular death in pediatric patients with CKD. These data are consistent with previous studies that showed CVD represents the most common [46] or the second most common [49] cause of death in the pediatric population. Moreover, it is clear from the literature that the atherosclerotic process starts already in the pediatric age

in high-risk situations, such as diabetes and familial hypercholesterolemia [50, 51]. Regarding CVD in children with CKD, much less information is available, but there seems to be growing evidence that they suffer from accelerated atherosclerosis, as observed in adult CKD patients [52]. These findings triggered great interest in this area, raising questions related to underlying co-morbidity conditions and modifiable risk factors that could attenuate the impact of the uremic state on cardiovascular disease. This subject achieves great importance not only in the pediatric but also adult investigation field, since ongoing advances on the management of children with CKD (such as technological advances in dialysis therapy or better management of co-morbidities) will undoubtedly lead to a growing number of patients who will be on dialysis or transplanted and who have been exposed to uremia since their childhood [53, 54].

Factors proven to contribute to atherosclerosis in the general population, such as dyslipidemia, left ventricular hypertrophy, diabetes mellitus, and hypertension are highly prevalent in adult CKD patients. Probably by extrapolation, these factors could apply to the pediatric CKD population as well. Children on conservative treatment, HD, and PD present high cholesterol and triglycerides levels [55], and the incidence of post-renal transplant hyperlipidemia is very high in long-term pediatric graft recipients [56]. Moreover, hypertension is present in 50 to 75% of uremic children [49].

A recent study in adults suggests, however, that the burden of traditional risk factors may not be sufficient to account for the higher mortality and morbidity from CVD in CKD, introducing the need for investigating non-traditional risk factors [57]. Markers of inflammation are the most important candidates in this list. Consistent with this, young adults with childhood-onset CKD have a surprisingly high incidence of arteriopathy associated with indicators of inflammation, hyperparathyroidism, calcium-phosphate overload, and hyperhomocysteinemia, even in the absence of traditional atherogenic risk factors [58].

The progression to a uremic state introduces anemia, calcium, and phosphorus disequilibria, increases insulin resistance, accumulates uremic toxins, and is also associated with intravascular volume overload, endothelial dysfunction, and worsening of hypertension. All of these conditions are predisposing factors for the acceleration of atherosclerosis also in the pediatric CKD population. In addition, markers of oxidative stress (antibodies to oxidized LDL, antioxidant activity) are elevated in children with CKD in the pre-dialysis stage [59], and vascular calcifications are highly prevalent even in young patients on dialysis [58, 60, 61].

The prevalence of malnutrition in adult CKD patients is reported to range between 30 to 60%, and throughout the years malnutrition has been constantly described as an important risk factor for mortality in these patients [62]. Also in children, protein energy-malnutrition is highly prevalent, and it becomes even more pronounced when dialysis treatment is initiated, since dialysis treatment is associated per se with increased catabolism, loss of nutrients, and anti-oxidants, as well as further dietary restrictions [63]. Malnutrition also contributes significantly to growth failure in children with CKD [64] through many factors, such as low protein and energy intake, anorexia, inadequate dialysis dose, metabolic acidosis, increased catabolic cytokines (TNF-$\alpha$ and IL-1), decreased anabolic hormones, and hyperleptinemia [64]. Furthermore, markers of nutritional status have been associated with increased morbidity and mortality in children with CKD [65, 66]. Wong et al. [67] have found that as patient height and linear growth scores decrease, the risk for death increases and children in the upper or lower extremes of BMI are at greater risk for mortality. They also conclude that abnormalities in the growth hormone (GH) and insulin-like growth factor (IGF-1) axis observed in children with CKD may increase the risk for death, particularly due to the decreased bioactivity of IGF-1, which has cardioprotective properties [67]. In addition, in accordance with data in the adult population, low serum albumin at the initiation of dialysis has also been shown to be an important marker for mortality risk in pediatric ESRD patients [65].

In general, maintaining an adequate nutritional intake in patients with many acute or chronic catabolic illnesses appears to improve their nutritional status and, at least in one study, reduce morbidity and mortality and improve quality of life [68]. The main problem when analyzing the effect of malnutrition on mortality in CKD patients is that the markers of nutritional status used in those studies may have been inaccurate. One example is related to serum albumin, which can be influenced by overhydration and particularly inflammation [69, 52]. The cytokine-driven acute phase response is activated in these situations, and albumin behaves as a negative protein in the response [70]. Therefore, it is impossible to discriminate in those studies if the impact of serum albumin levels was related to malnutrition or to the chronic inflammation state. Additionally, subjective global assessment (SGA), which is also used as a tool to evaluate nutritional status, may be an indicator of the degree of co-morbidity and not only a nutritional status marker. Based on these findings, we have proposed that at least two types of malnutrition may be present in CKD patients [71]. Whereas type-1 malnutrition is associated with the uremic syndrome per se, the other cytokine-driven type of malnutrition (type-2) is often associated with significant co-morbidity. It is obvious that in the clinical setting these two types of malnutrition may often be combined. The validity of this concept still needs to be assessed in the pediatric population.

## Conclusion

In conclusion, it is proposed that complications of CKD are highly influenced by the high prevalence of inflammation, which reflects a broad array of pathogenic factors. Interestingly, inflammation-induced tissue response mimics an accelerated process of ageing. Inflammation is exaggerated in both adults and children with CKD, and it is closely related to malnutrition, which may rarely be the

direct cause of death, but may contribute to a poor prognosis by reflecting or aggravating pre-existing inflammatory status, heart failure, accelerating atherosclerosis, and increasing the susceptibility to infections [4]. For the future, it is crucial to investigate how malnutrition, inflammation, and CVD are interrelated in pediatric CKD patients. Since early identification may allow for the most efficient strategies for prevention and treatment of complications of CKD, the pediatric population certainly deserves special attention in future studies.

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