Review

# Immune Response as a Mechanism of the Initiation and Progression of Chronic Kidney Disease: From the Inflammation to Immunosenescence

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**Keywords**. chronic kidney disease, immune system, inflammation

Chronic kidney disease (CKD) is a common disease in the world that has adverse outcomes. Immune system and its components have important role in the initiation, progression and complications of this disease by systemic inflammation. Regarding the role of kidneys in the body's natural homeostasis and its relationship with other organs, CKD causes impairments in other organs. Patients with chronic renal failure have variety of complications, such as cardiovascular disease, anemia, bone disorders, immune dysfunction and etc., together which culminate in the morbidity and mortality of these patients. Immune dysfunction is one of the most important and serious complications in CKD patients. These patients often suffer from immune suppression and are susceptible to some infections. In this review, we describe some major findings of interactions between the kidney and immune system in CKD.

IJKD 2019;13:283-99
www.ijkd.org

## INTRODUCTION

Kidney diseases are commonly classified as either chronic or acute. Acute kidney injury (AKI) is resulted usually from interactions between trauma, bacterial infection, sepsis, or ischemia reperfusion injury that can convert to chronic renal disease. Acute kidney injury increases the risk of end-stage renal disease development. Chronic kidney disease (CKD) is usually caused by diabetic complications, hypertension, metabolic syndrome, and autoimmune disorders.[1] Approximately 10%–15% of populations suffer from CKD in different countries.[2] Chronic kidney disease also defined by persistence of renal damage for more than three months.[3] CKD classified into five stage according to estimated glomerular filtration rate (eGFR): more than 90 mL/min per 1.73 m² (stage 1: Kidney damage with normal GFR), 60–89 mL/min per 1.73 m² (stage 2: mild), 30–59 mL/min per 1.73 m² (stage 3: moderate), 15–29 mL/min per 1.73 m² (stage 4: severe), and less than 15 mL/min per 1.73 m² (stage 5: renal failure).[4] This disease eventually leads to a reduction in the volume of urine, renal failure and accumulation of toxins. The patients with renal failure or end-stage renal disease (ESRD) are required dialysis or kidney transplantation. CKD patients usually initiate dialysis in stage 5 CKD.[5]

CKD is manifested by several complications,[6] including cardiovascular disease, hypertension,

acute kidney injury, anemia (which is non-responsive to treatment), bone disorders, depression, frailty and immunodeficiency (leading to susceptibility to infections and inefficient response to vaccines).[7] Immune system dysfunction is one of the serious complications of CKD. On the other hand, the immune system has a central role in the initiation and progression of this disease by promoting and persistence of systemic inflammation.[1] Previous studies have emphasized understanding the important involvement mechanisms, especially with respect to immune system, in CKD. In this review article, we aimed to go through the implications of an immune system in the initiation, perpetuation, and complications of CKD.

## INNATE IMMUNE RESPONSE IN CKD

Innate immunity is the first line of defense against infections and is activated rapidly before the adaptive immune responses. Innate immunity is characterized by responses against specific pathogen-associated molecular patterns (PAMPs) for example LPS and damage associated molecular patterns (DAMPs) like high-mobility group box 1 (HMGB1) and ATP.[8] In CKD, renal necrotic or apoptotic cells release DAMPs and chemotactic factors into the extracellular space, where they are recognized by pattern recognition receptors (PRRs) like Toll like receptor (TLRs) and NOD like receptor on innate immune cells, which causes production of inflammatory mediators and recruit further immune cells, leading to renal immunopathogenesis.[9] Immune cells also are important for the repair of renal tissue damages and regulate the restoring process.[10] The key components of innate immunity involved in the development of renal disease are TLRs, dendritic cells (DCs), polymorphonuclear (PMN) leukocytes, monocytes, macrophages, natural killer (NK) cells and the complement system.[1]

The tubular epithelial cells and endothelial cells of the kidney, by expressing TLR1 to TLR6 and NOD-like receptors (NLRs), can recognize DAMPs within the kidney microenvironment, and therefore promote innate immune responses and subsequent renal inflammation.[11] TLRs and related signaling adaptor proteins like Myeloid differentiation primary response 88 (MyD88), nuclear factor (NF)-κB play key roles in the severity of CKD and inflammatory responses by induction of IL-1β and Il-18.[12-15]

Several immune cells are present in the kidneys, including DCs, macrophages and a few lymphocytes.[16] Kidney DCs are existed in the tubular epithelium and the peritubular capillaries and have the main role in the regulation of the function of T cells, B cells and NK cells, defense against microbial agents, homeostasis, local injury and inflammation.[17] DCs are also involved in establishing immune tolerance to self-antigens. Renal DCs capture the low-molecular-mass proteins like food antigens and hormones, which are reabsorbed and degraded by tubular epithelial cells. Then, these antigens are transferred into renal lymph nodes to be cross-presented to $CD8^+$ T cells, eventuating in the expression of programmed cell death 1 ligand 1 (PDL1), which cause apoptosis of these T cells.[18,19] In renal damage, DCs are recruited rapidly and accelerate tissue injury by increasing the in cable of phagocytosis and producing pro-inflammatory cytokines and chemokines, leading to infiltration of further immune cell, such as neutrophils. Actually, DCs can play main roles in impairment of immune cells balance, which relate to increasing of cardiovascular risk in CKD patients.[20-22] Another study demonstrated that renal DCs induce apoptosis and the generation of alloantigens within 24-hour following acute kidney injury by releasing TNF-α. This cytokine cause enhances leukocyte extravasation by binding to native renal endothelial cells and upregulating adhesion molecules.[23]

Neutrophils are first cell types that migrate to the renal interstitium within less than few hours after injury.[23] Increased number of circulating PMNs has been related to decreased renal function in CKD patients.[24] A study reported that PMNs in hemodialysis patients upregulated expression of TLR-4, TLR-2, CD11b, and CD18, increased production of reactive oxygen species (ROS) that cause prevailing systemic oxidative stress, inflammation and tissue damage in these patients.[25]

The oxidative stress promotes the generation of TLR ligands, which can induce monocytes, particularly $CD14^{++}CD16^+$ (pro-inflammatory subtype) and $CD14^+CD16^{++}$ (non-classical subtype), to be released from bone marrow.[17,26] In CKD, monocytes upregulate the expression of TLR-2, TLR-4, and cell surface integrin that leads to increased production of cytokines and

ROS.[25] Kidney injury can active the renal sentinel immune cells (known as mononuclear phagocyte cells). Following activation, they differentiate to inflammatory phenotype characterized by marked expression of the surface glycoprotein lymphocyte antigen 6 complex locus C ($Ly6C^{high}$). These cells produce inflammatory mediators such as IFN-ɣ, IL-6 and free radicals, which accelerate inflammation by recruiting of further immune cells to injury niche.[10]

Macrophages are commonly found in the renal medulla and capsule,[27] and exert a key role in inflammation and immune modulation. They have controversial role in physiological and pathophysiological condition due to CKD.[28] Macrophages are commonly classified into two main subtypes, M1 (pro-inflammatory macrophages) and M2 (anti-inflammatory macrophages). M1 macrophages recognize danger signals by PRRs, thus result in the secretion of pro-inflammatory cytokines like interleukin (IL)-1, IL-6, IL-23, and ROS.[29,30] Each of them was correlated with impaired renal function and infiltration of other immune cells like neutrophils, monocytes, NK cells and T helper (Th) 1/17 cells to the site of injury.[31-3] In sterile kidney injury (absence of PAMPs such as exposure to nephrotoxins), more inflammatory macrophages infiltrate into the involved site [34]. Pro-inflammatory macrophages also release matrix metalloproteinases (MMPs) that trigger renal fibrosis.[33] This process causes persistent inflammation, causing an increase in the M1:M2 ratio and CKD progression. M2 macrophages contribute to resolving inflammation via stimulating angiogenesis and wound healing.[35] If inflammation continues and does not resolve, M1 macrophages remain at injured sites, the balance of M1/M2 disrupt and M2 macrophages switch to M1, leading to fibrosis promotion and renal failure.[36] Ding X.Y *et al* reported M1 macrophages and their markers increase and M2 polarization impairs in an animal model of CKD.[37]

NK cells are another cytotoxic leukocytes, which can recognize and kill stressed cells directly in the absence of major histocompatibility complex (MHC) receptors and antibodies.[23] Renal NK cells can induce activation of macrophages via secretion of interferon (IFN)-γ[38] and, thereby, participate in AKI.[39] Indeed, NK cells have important role in chronic autoimmune renal diseases. They can be stimulated by DCs and release cytokine, like IFN-γ, and eventually promote renal disease progression.[40] Following kidney injury, renal tubular epithelial cells (TEC) produce osteopontin, which can attract NK cells to the niche of injury and cause renal dysfunction.[23]

### Complement System

Aside from immune cells, complement system participates in the pathogenesis of CKD. The complement system consists of over 30 serum proteins that act as cascade and generate membrane attack complex to eliminate pathogens. The pathways of complement activation are divided into classical, alternative, and lectin pathways.[41] The complement activation in CKD may alter renal cell function and contribute to chronic injury. They also can induce the release of a range of pro-inflammatory and profibrotic mediators such as chemokines, cytokines, growth factors and matrix proteins.[42] Modified C3 can activate the alternative pathway[43] and, therefore; cause urine acidification.[44] In addition, decreased expression of CD59 on surface of tubular cells[45,46] and release of anaphylatoxins can also cause uncontrolled activation of complement.[47,48] As complement system is involved in tissue repair and fibrosis,[49] uncontrolled activation of this system results in the progression and maintenance of CKD.

## ADOPTIVE IMMUNITY RESPONSE IN CKD

T lymphocytes (cell-mediated immunity) and B lymphocytes (humoral/antibody-mediated immunity) are two main components of the adaptive immune system. Two major T cells types include $CD8^+$ cytotoxic T cells and $CD4^+$ T helper (Th) cells. The functions of $CD8^+$ T cells are similar to NK cells and their role is to destroy infected and tumor cells.[1] Cytotoxic T cells have a complex role in CKD. They can be activated by specific renal autoantigens, leading to local injury and inflammation. In other words, activated $CD8^+$ T cells recruit more $CD8^+$ T cells and, therefore, cause further renal damage via release excess renal specific autoantigens.[50]

$CD4^+$ T cells are also one of the main players in cellular immunity that are activated by antigen presenting cells (APCs) and inflammatory cytokines. Th cells are divided into several major subtypes based on the primary function and cytokine production, including Th1 (154), Th2 (154), Th17

(87), and regulatory T (Treg) cells.[51-3] Th1 cells are specified by the generation of inflammatory cytokines, such as IFN-γ, IL-2, lymphotoxin-α, and tumor necrosis factor (TNF)-α that promote activation of macrophages, neutrophils, $CD8^+$ T cells and tissue damage.[54] Th2 cells, however, are characterized by secretion of anti-inflammatory cytokines like IL-4, IL-5, and IL-10. They can downregulate Th1 cells and suppress classic activation macrophages.[55] Renal tubular cells express the chemokine IL-16, which attract Th1 and Th2 cells to kidney and have main roles in the transition from AKI to CKD.[23] In addition, Th2-polarized cells have several roles in immune regulation and humoral immunity that are associated with the production of autoantibodies in autoimmune disorders.[54] The balance between Th1 and Th2 determines the progression of atherosclerotic lesions in hemodialysis patients.[56] Renal tissue can release hidden antigens, which recognize by autoreactive T cells. This event may relevant to sustaining immune cells and inflammation in the site of injury.[10] Hsu et.al reported that Th17 cells are increased and regulatory of T cells diminished in CKD patients. The imbalance in Th17/Treg ratio related to progression of acute cardiovascular events.[26] The $CD4^+CD25^+FoxP3^+$ Treg cell subset secretes cytokines like transforming growth factor (TGF)-β and IL-10. The primary function of these cells is to suppress the adaptive immune system function and maintain self-tolerance and, therefore, protection against autoinflammatory diseases.[57] In other words, Treg cells have protective role in renal injury and expansion of Treg population can delay the renal injury and modulate spontaneous renal inflammation associated with the autoimmune disorder.[58,59] An animal study showed that depletion of Treg cells cause severe AKI, and decrease tubular recovery by both increased proliferation of T cells and cytokine levels.[60] The study of Zhang *et al.* demonstrated an imbalance of Th17/Treg in uremic patients, which was correlated with the development of acute cardiovascular diseases, consequently chronic renal disease.[61] Another subtype is $CD4^+CD28^-$ T cells that act as pro-inflammatory cells and produce high concentrations of IFN-γ, IL-2, TNF, and are cytotoxic. The number of these cells is increased in patients with stage 5 CKD[62] and facilitate destabilization of atherosclerotic plaques that contribute to increased complications in CKD patients.[63]

NKT cells are another immune cells which express both T cell receptors and the NK receptor. The main roles of NKT cell are unclear. Some of them are proinflammatory cells and involve in inflammation processes, whereas some of NKT cells have protective roles. NKT cells can activate neutrophils and the production of cytokines such as IFN-γ in tubular injury.[23]

There are little studies about role of B cells in CKD pathogenesis. But it seems that the IgM antibodies limit kidney repair in animal models and the depletion of B cells result in improve kidney repair.[23] Jang *et al* reported that the number of B cells increase in renal injury and impair kidney repair.[64]

Cooperation between innate and adaptive immune cells has been seen in different types of kidney disease. For example, the innate/inflammatory cells can generate mediators like cytokines, chemokines, eicosanoids, and ROS, which upregulate adhesion molecules, thereby culminate in renal injury by recruiting more innate/adoptive cells.[65,66] In cardiovascular disease, there is a complex link between renin–angiotensin–aldosterone system, T H17 cells and mononuclear phagocytes that are involved in hypertension and systemic inflammation, contributing to CKD complications.[9]

## CYTOKINES AND INFLAMMATORY MARKERS IN CKD

Inflammation, which is a general feature of CKD, is an important tool for prognosis and diagnosis of this disorder.[67] Inflammatory markers and cytokines have critical roles in the initiation and perpetuation of renal injury.[1] In the pathogenesis of the renal disease, cytokines trigger the production and activation of endothelial cell adhesion molecules and chemokines that promote more renal immune cell infiltration and inflammation.[68,69] This process results in the development of local oxidative stress, impairing both renal tubular and hemodynamic function, the generation of profibrotic factors and the progression of CKD.[1,70]

The several factors may underlie the impression of inflammation in complications from patients with chronic renal failure,[56] such as increased inflammatory cytokine level, oxidative stress, production of modified plasma proteins, dialysis

process and infectious diseases.[71] Many studies demonstrate that cytokines and inflammatory mediators can directly alter renal function and result in systemic inflammation.[72-4] The serum level of albumin is the main indicator of nutritional status and also a negative inflammatory marker. Our previous data showed that low serum albumin was a risk factor of anemia in hemodialysis patients, and also could be considered to be a predictor of treatment response of anemia.[75] Some of the inflammatory markers that play key roles in the pathogenesis of CKD are listed in Table 1.

**Table 1.** Inflammatory Markers Involved in CKD Patients

| Category | Marker | Role in CKD | References |
|---|---|---|---|
| Short Pentraxins | C-reactive protein (CRP) | Independent risk factors for all-cause mortality in CKD/predictor of serum albumin level in dialysis patients/associated with faster kidney function loss | 75, 151, 152 |
| | Serum amyloid P (SAP) | Increased SAP in hemodialysis patients related to pathogenesis of renal diseases | 153 |
| Long Pentraxins | Pentraxin-3 (PTX3) | Increased PTX3 levels are associated with lower GFR and independently predict incident CKD/strong independent links with endothelial dysfunction and albuminuria/positive association with fibrinogen/rapid marker for inflammation | 154-157 |
| Pro-inflammatory Cytokines | Interleukin (IL)-1β | Role in inflammasome and inflammation | 158 |
| | IL-6 | Have a greater effect than albumin in predicting mortality/a better prognostic marker than CRP/strong predictor of hypoalbuminemia, hypocholesterolemia and mortality | 93, 134, 159 |
| | IL-8 | Independent predictive factor for cardiovascular and mortality | 160 |
| | IL-12 | Roles in the pathogenesis of renal disease | 1, 113 |
| | IL-17 | roles in the pathogenesis of renal disease | 161 |
| | IL-18 | Increased IL-18 related with complications of CKD/A direct correlation between IL-18 levels and time on dialysis | 162 |
| | Tumor necrosis factor (TNF)-α | Associated with an increased risk for mortality CKD patients/↑TNF-α correlate with decreased renal blood flow and GFR | 163, 164 |
| | Interferon (IFN)-γ | Roles in the pathogenesis of renal disease | 1 |
| Anti-inflammatory Cytokines | IL-4 | Unknown | 73 |
| | IL-10 | Unknown | 73 |
| | TGF-β | Influence on GFR<br>Increased TGF-b induce renal disease by accumulation of matrix proteins and mesangial expansion | 90<br>165 |
| Adhesion Molecules | Intercellular adhesion molecule-1 (ICAM-1) | Upregulated in chronic inflammatory states, and considered as an expression of endothelial dysfunction in CKD | 166 |
| | Vascular cellular adhesion molecule-1 (VCAM-1) | Upregulated in chronic inflammatory states, and considered as an expression of endothelial dysfunction in CKD | 166 |
| | E-selectin | Markers of endothelial dysfunction/role in the development of CKD | 158 |
| | P-selectin | markers of endothelial dysfunction/role in the development of CKD | 158 |
| Inflammatory Molecules with Negative Acute-phase Reaction | Albumin | Decreased albumin in hemodialysis patients/predictor of anemia and unresponsiveness to treatment of anemia/marker of nutritional status in dialysis patients/associated with morbidity and mortality in hemodialysis patients | 167 |
| | Transferrin or TIBC | Decreased transferrin in CKD | 168 |
| | Fetuin-α | Increased fetuin-α link to mortality and cardiovascular events in PD patients | 169, 170 |
| Oxidative Stress Molecules | Reactive oxygen species (ROS) | Roles in the pathogenesis and progression of CKD | 171, 172 |
| Mineral Element and Vitamins | Iron | Increased iron disrupts the functions of innate immune cells | 116, 117 |
| | Calcium | Increased calcium in hemodialysis patients and associated with high CRP concentrations | 173, 174 |
| | Potassium | Increased potassium in hemodialysis patients/important factors for cardiovascular events and mortality in CKD | 173, 175 |
| | Vitamin D | Decreased vitamin D related with increased inflammatory and platelet activity and increased mortality in CKD patients/Vitamin D therapy may reduce the progression of CKD/ | 176, 177 |

**Table 1.** (Continued)

| Category | Marker | Role in CKD | References |
|---|---|---|---|
| Coagulation Markers | Fibrinogen | Correlated with CRP and an independent cardiovascular risk factor in CKD | 72 |
| | Fibrin D-dimer | Contribute to endothelial dysfunction and progression of atherosclerosis | 178 |
| | Von Willebrand (vWF) factor | markers of endothelial dysfunction/role in the development of CKD | 158 |
| | Coagulation factor VII | Contribute to endothelial dysfunction and progression of atherosclerosis | 178 |
| | Coagulation factor VIII | Contribute to endothelial dysfunction and progression of atherosclerosis | 178 |
| Pro-inflammatory Transcription Factors | Nuclear factor (NF)-κB | Increased expression in the kidneys diseases | 179 |
| | Activator protein (AP)-1 | Increased expression in the kidneys diseases | 180 |
| Lipoproteins | High density lipoprotein (HDL) | Decreased with inflammation in CKD | 75 |
| | Low density lipoprotein (LDL) | Decreased with inflammation in CKD | 75 |
| | Cholesterol | Decreased with inflammation in CKD | 75 |
| Molecules Related Adipose Tissue | Adiponectin (ADPN) | Related to several metabolic risk factors/have a protective role for the cardiovascular system among dialysis patient | 181 |
| | Resistin | Increased resistin in CKD/role in stimulating the synthesis and release of pro-inflammatory cytokines in CKD | 182 |
| | Leptin | Increased leptin in CKD correlate with C-reactive protein levels<br>May has main role in the pathogenesis of inflammation-associated cachexia in CKD | 183 |
| | CD163 | A marker of mature macrophages<br>Increased in CKD | 184 |
| Growth Factors | Fibroblast growth factor (FGF) 23 | Increased FGF23 in CKD/<br>associated with adverse clinical outcomes | 185 |
| | Insulin like growth factor (IGF)-1 | Influence cardiovascular complication in chronic renal failure | 186 |
| Other Inflammatory Marker | Serum amyloid (SA)-A | Predictor of serum albumin level in dialysis patients | 187 |
| | Serum ferritin | Increased serum ferritin levels in CKD patients and reflect inflammation status and may indicate iron overload | 188 |
| | Platelet lymphocyte ratio (PLR) | Predictor of inflammation in ESRD | 189 |
| | Neutrophil lymphocyte ratio | Increased in high-risk patients with CKD | 98 |
| | White blood cell count | Role in CKD | 190 |
| | Uromodulin | Decreased uromodulin in CKD related with aggravates urinary tract infections, crystal aggregation and reduced cytokine elimination/ contribute to the systemic inflammation in CKD | 191, 192<br>193 |
| | Asymmetric dimethylarginine (ADMA) | Progression of asymptomatic and symptomatic atherosclerosis in patients with CKD of all stages | 194, 195 |
| | creatinine | Important predictor of mortality in ESRD/serum creatinine have been associated with a longer hospital stay and higher hospitalization rates | 99, 168 |
| | BNP | Strong association with cardiovascular dysfunction in CKD patients | 196 |
| | cardiac troponin T (cTnT) | A biomarker for mortality risk stratification in ESRD/marker of prognostication Kidney Disease | 197 |
| | Proteinuria | Associated with endothelial dysfunction | 198 |

**Table 1.** (Continued)

| Category | Marker | Role in CKD | References |
|---|---|---|---|
| | Plasma triiodothyronine (fT3) | Decreased in CKD and ESRD patients<br>markers of inflammation and endothelial activation<br>Strong predictor of adverse clinical outcomes of death and is associated with inflammation and cardiovascular damage/ strongly correlated with systemic inflammatory markers and are an independent predictor of mortality in CKD | 199, 200 |
| | Hepcidine | A polypeptide that regulates iron homeostasis and serve as an indicator of functional iron deficiency in ESRD patients/role in the pathophysiology of anemia associated with chronic diseases and erythropoietin resistance | 201 |
| | macrophage inhibitory cytokine-1 (MIC-1/GDF15) | predicts atherosclerotic events independently of traditional risk factors/<br>A novel independent serum marker of mortality in CKD | 202 |
| | Serum mannose binding lectin (MBL) | Increased MBL in hemodialysis patients associated with management of patients and prediction of kidney allograft survival | 141, 203 |
| | asymmetric dimethylarginine (ADMA), symmetric dimethylarginine (SDMA) | Increased ADMA and SDMA accelerate endothelial dysfunction and renal impairment by inhibition of nitric oxide (NO) synthesis and TGF-β expression | 204 |
| | Neutrophil Gelatinase-Associated Lipocalin (NGAL) | NGAL increase in following tubulointerstitial damages and is a good predictor for detection of changes in GFR | 205 |
| | Omentin (an adipocytokine) | Increased omentin in hemodialysis patients /positively correlated with a number of cardiovascular risk factors and inflammation | 206 |

## CKD AND INFLAMMATION

Inflammation causes an alteration in renal hemodynamics that can continue upon hours to years.[76] Although the footprint of the immune system has been seen in all stages of CKD, the exact underlying mechanisms are not clear. Inflammation is initiated by the infiltration, and accumulation of immune cells at the site of injury, resulting in release of soluble mediators or cytokines in response to local cell stress.[77]

The relevance of inflammatory mediators to renal dysfunction depends on the persistence of inflammation, the pathological state, and the site of inflammation.[1] Persistent of sterile inflammation has been associated with accumulation of profibrotic cells like myofibroblasts, mast cells, macrophages, eventuating in more production of the extracellular matrix and renal fibrosis.[78-80] Tissue damages cause releasing of DAMP molecules, which may activate TLRs, thereby amplify the inflammatory process and tissue remodeling.[78]

Studies implicated the importance of TLR-2 and TLR-4 in the development of inflammation and fibrosis by stimulating the production of proinflammatory mediators, such as IL-8, TNFα, and IL-1.[81,82] The NLRP-3 inflammasome recognizes alarming signals like ROS, uric acid, ATP, nucleic acids, and extracellular matrix components in kidney diseases.[83-5] In this scenario, renal inflammation ultimately results in declined renal blood flow and clearance.[86,87] On the other hand, decreased GFR leads to accumulation of uremic toxins, which can affect immune system via the production of advanced glycation end (AGEs), which are nonenzymatically glycated and oxidized proteins that have been implicated in diabetes related-complications. AGEs cause a marked reduction of renal clearance ability and promoting inflammation through increased oxidative stress.[88] Understanding the role of inflammatory mediators in renal hemodynamic function contributes to design therapies in these patients.[89-91]

### The Role of Inflammation in Progression of CKD

Changes in glomerular hemodynamics and proteinuria trigger immune cell migration into the inflamed site, phenotypic conversion of epithelial cells and lymphocytes into fibroblast, leading to fibrosis and progression of CKD and end-stage renal disease (ESRD).[1,92] During progressive renal

disease, cytokines, such as IL-1, IFN-α, IFN-β, IFN-γ, platelet-derived growth factor (PDGF), TNF, TGF-α and TGF-β are upregulated and predict the clinical features of the progressive disease.[93-5] It has been shown that TGF-β released from macrophages and tubular cells is important regulator in generation of extracellular matrix proteins.[89,90] Type and production rate of fibrotic proteins from fibroblasts determine the tissue scarring and renal damage.[96,97]

### The Role of Inflammation on CKD Complications

CKD complications can occur at any stage.[6] Kato *et al*. reported cardiovascular disease and infections as two common types of CKD complications, causing high rate of mortality by induction of chronic inflammation.[98] Although decreased erythropoietin production is the main cause of anemia in CKD,[99] cytokines such as TNF, IL-1, IL-6, TGF-β, and IFN-γ are additional contributing factors.[100] Frailty in CKD patients is related to low serum levels of hemoglobin, increased levels of parathyroid hormone and low levels of serum vitamin D.[101] Malnutrition-inflammation-atherosclerosis (MIA) syndrome is another disease that has a high prevalence in CKD patients and is a non-classical risk factor for CKD.[102] This syndrome can aggregate inflammation, accelerate atherosclerosis and increase susceptibility to infection.[103] A defect in almost all immune cell populations, increased susceptibility to infection and poor response to vaccination have been correlated with decreased GFR and accumulation of uremic toxins in patients with CKD and ESRD. For this reason, these patients should be vaccinated in early stages, particularly against influenza, hepatitis B, pneumococcus, and varicella.[104] Immunodeficiency might also be nontraditional risk factors for cardiovascular disease and malignancies in these patients.[105]

### The Role of Inflammation in Mortality of Patients with CKD

Inflammation can also cause mortality by advancing vascular calcifications and endothelial dysfunction.[106] In addition, several inflammatory biomarkers, such as C-reactive protein (CRP), IL-6, fibrinogen, leukocytosis, mannose-binding lectin (MBL), and genetic variations in genes related to immune response predict the progression of complications and mortality in these patients.[82]

## IMPACT OF CKD ON SYSTEMIC IMMUNITY

There is a reciprocal relationship between kidney diseases and the immune system. Renal failure leads to release of PAMPs, DAMPs, and inflammatory factors into the circulation that has been associated with mortality and morbidity in these patients.[107-112] Proteinuria, malnutrition, iron overload, alternation of vitamin D level, dialysis processes, chronic inflammation, disruption in the balance between the production of free radicals and antioxidant defenses and uremic toxin affect the immune system.[26,113] Proteinuria has a crucial role in immune system by reducing many immune components, like adaptor proteins and antibodies.[1] CKD reduces bone marrow cell proliferation, leading to decreased number of immune cells and anemia[114,115]. Iron overload as a consequence of excessive intravenous iron administration disrupts phagocytic activity and microbial killing capability of macrophages and neutrophils,[116,117] $CD4^+$ T cell depletion and expansion of $CD8^+CD28^-$ T cells.[118] Another complication of elevated iron levels is the development of pro-inflammatory M1 macrophages, which cause augmentation of local inflammation, oxidative stress, and inhibition of injury healing; all of them can contribute to atherosclerosis and CKD progression.[119] Alteration of vitamin D and parathyroid (PTH) hormone levels results in dysfunction of immune cells. Increased PTH levels cause raising cytosolic calcium concentrations, which in combination, decrease PMN phagocytosis capacity, B cell proliferation and antibody production.[120] Since the renal tubules are the site of active vitamin D synthase, vitamin D deficiency maybe occur at any stage of kidney disease.[121] A study showed that the vitamin D receptor is downregulated in early stages of renal disease.[122] Vitamin D is a potent immunomodulator and plays an important role in controlling immune effector responses, especially during infection or vaccination, by repressing the production of Th1-related cytokines and suppression of inflammatory macrophages.[123,124] It also can inhibit all of the inflammation processes involved in the pathogenesis of CKD.[125] Vitamin D deficiency may be related to reduced survival in the CKD patients in stages 3 to 5 of the disease.[126] Malnutrition, iron overload, increased intracellular calcium, dialysis process, and uremic

toxins are involved in the dysfunction of PMN, T lymphocyte, and monocytes.[127,128] Prolonged dialysis is associated with developing infective endocarditis, peritonitis, and pneumonia, which are risk factors for mortality in hemodialysis patients by decreased phagocytic function.[129-131] In order to prevent infections, it is recommended these patients should be vaccinated against common infectious diseases.[132,133] Increased number of Th17 cells and decreased number of Treg cells were also observed patients undergoing hemodialysis (136). The persistent systemic inflammation culminates in the immunosuppressed state in CKD.[134] Many studies have indicated that uremia can alter both innate and acquired immune systems in these patients. For example, endocytosis and maturation of monocytes and monocyte-derived DCs are impaired in CKD patients.[135] Uremia can also decrease the functions of APCs like DCs and macrophages by modulating the costimulatory molecules (CD80, CD86) and downregulating TLR expression.[136,137] NK cells counts are diminished and also there are modulated phenotypic, cytotoxic and migratory features in hemodialysis patients, which are associated with the incidence of cardiovascular, cancer, infection and pregnancy disorders in uremic patients.[138] The density of Langerhans cells in the skin of uremic patients is reduced that might contribute to the reduced vaccination responses in these patients. The numbers of $CD14^{+}CD16^{++}$ monocytes and $CD4^{+}CD28^{-}$ T cells are increased that could explain the high incidence of cardiovascular disease in ESRD patients.[139] Serum MBL level is declined in peritoneal dialysis and hemodialysis patients and

**Table 2.** Effects of CKD on Immune System

| Immune Cell | Alterations | Clinical Outcome | References |
|---|---|---|---|
| Neutrophils | Increased of numbers<br>Increased ROS and cytokine production<br>Increased apoptosis<br>Upregulation of TLR 2/4, and integrin expression<br>Increased of CD11b and CD18b expression<br>Spontaneous activation and degranulation<br>Decreased phagocytosis capacities | Increased of inflammation and renal damage | 207-209 |
| NK Cells | Increased activity<br>Decreased of numbers<br>Decreased expression of activation receptors | Decreased tumor immune surveillance | 138, 210 |
| Monocytes | Increased circulating CD14+CD16+ monocytes<br>Increased ROS and cytokine production<br>Upregulation of TLR 2/4 and integrin, SA-A and CD36 expression<br>Spontaneous activation and degranulation<br>Decreased phagocytosis capacities | Increased of inflammation and renal damage/<br>Increased risk for CVD | 135, 211 |
| Macrophages | Delayed clearance of microbial<br>Spontaneous activation and degranulation<br>Decreased phagocytosis capacities | Increased of inflammation and renal damage | 212, 213 |
| DC | Depletion of antigen presenting cells<br>Increased of mDC/pDC ratio<br>Decreased costimulatoty molecules | Decreased T cell dependent immune respons/<br>Decreased vaccination response | 136, 137 |
| γδ T Cells | Unknown | Unknown | 208 |
| Effector T Cells | Increased of TH 2 and TH 17<br>Increased production of 2,3-dioxygenase<br>Increased production of arginase type-1<br>expansion of CD4+CD28– T<br>Increased apoptosis<br>Shortened of telomere length<br>Reduced CD4/CD8 T-cell ratio<br>Decreased memory T cells | Decreased vaccination response/<br>Increased risk for severe infections, CVD and cancer/<br>Pro-inflammatory milieu | 214-216 |
| Regulatory T Cells | Increased apoptosis<br>Decreased regulatory T (Treg) cells<br>Decreased suppression activity | Unknown | 217 |
| B Cells | Increased apoptosis<br>Increased production of pro-inflammatory cytokines<br>Decreased B-cell number<br>Downregulation of BAFF receptor<br>Decreased antibody production | Decreased humoral responses | 144, 145 |

probably is accompanied by increased susceptibility to infection.[140] Our study demonstrated that increased MBL level in hemodialysis patients was associated with the management of patients and prediction of kidney allograft survival.[141] Patients with chronic hemodialysis had lymphopenia and diminished numbers of both CD4 and CD8 T cells and their proliferative response upon stimulation was decreased.[142] The maturation of subsets of Th cells is impaired in hemodialysis patients that maybe due to protein-energy wasting (PEW).[143]

CKD patients also have lower percentages of peripheral B cells by increased incidence of apoptosis in B cells and downregulation of BAFF receptor;[144,145] they also have increased apoptosis rate and depleted populations of naive and central memory T cells by decreased expression of the anti-apoptotic molecule Bcl-2, IL-7 deficiency, increased expression of IL-2 receptors.[113,146,147] Increased suppressor activity of T cell has been observed in uremic patients.[148] Uremia is accompanied by reduction in the number and function of lymphoid cells, whereas numbers of myeloid cells are normal or increased. Patients with ESRD manifest increased numbers of specific pro-inflammatory subsets of T cells and monocytes.[105] Therefore, an immunosenescent state occurs in CKD patients, implying that lymphoid lineage is skewed toward myeloid lineage, the function of activated immune cells is decreased and cytokines expression are altered, a phenomenon that is known as tachyphylaxis.[149,150] As mention above, these patients suffer from acquired immunosuppression, in which the immune system loses its normal function, leading to poor vaccination response and a high incidence of infection and malignancy.[111] Effects of CKD on immune system are shown in Table 2.

## CONCLUSION

The correlation of the immune function and inflammation with renal function has widely been investigated. Activation of TLRs, NLRs, inflammasome and other immune components to respond to pathogens or DAMPs leads to chronic inflammation and fibrosis development. Inflammatory mediators play major role in renal hemodynamics, water and salt homeostasis, and blood pressure control. Inflammation can also contribute to cardiovascular diseases, diabetes, trauma, infections, resulting in significant renal pathogenesis. Uncontrolled inflammation causes glomerular, tubular, and interstitial damage. This inflamed milieu can significantly be relevant to acute and chronic kidney diseases. On the other hands, the immune dysfunction as a complication is arising from chronic inflammation and considers being a major challenge in this disease. These findings demonstrate how immune responses link inflammation, the progression of fibrosis and their complications. Not surprisingly, targeting the immune system and inflammation could be novel therapeutic approach for improving outcomes and decreased patient morbidity and mortality. The mediators of immune system can also be used as useful diagnostic or prognostic tools to differentiate various stages of the CKD and monitoring of treatment regiments.

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Received April 2019
Revised July 2019
Accepted August 2019