ISSN 0975-2366
DOI:https://doi.org/10.31838/ijpr/2021.13.02.058

Review Article

A Narrative Review: The Inflammation in Chronic Kidney Disease (CKD)

DEDI RACHMADI[1], MOHAMMAD RUDIANSYAH[2*], RIA BANDIARA[3], LEONARDO LUBIS[4]
[1]Division of Nephrology, Department of Pediatric, Faculty of Medicine, Universitas Padjadjaran / Hasan Sadikin Hospital Bandung, Indonesia
[2]Division of Nephrology & Hypertension, Department of Internal Medicine, Faculty of Medicine, UniversitasLambung Mangkurat / Ulin Hospital Banjarmasin, Indonesia
[3]Division of Nephrology & Hypertension, Department of Internal Medicine, Faculty of Medicine, Universitas Padjadjaran / Hasan Sadikin Hospital Bandung, Indonesia
[4]Department of Anatomy, Physiology, and Cell Biology, Faculty of Medicine, Universitas Padjadjaran Bandung, Indonesia
*Corresponding author:
Email: rudiansyah@ulm.ac.id
Received: 13.11.20, Revised: 05.12.20, Accepted: 25.01.20

ABSTRACT
The chronic kidney disease (CKD) is a serious health challenge within every community, with a rising prevalence in recent years. The contribution of the immune system and the inflammatory process is increasingly recognized as the beginning of CKD pathophysiology. Risk factors such as glomerulonephritis, lupus nephritis, diabetes mellitus, hypertension, and obstructive nephropathy also contribute to the progression of inflammation in CKD. Inflammation that occurs is triggered by both innate immunity and adaptive immunity. Inflammatory response that is related to adaptive immunity in CKD can be either cellular immunity or humoral immunity, in which they can produce pro-inflammatory mediators. Pro-inflammatory mediators can alter renal hemodynamics, sodium and water homeostasis, and blood pressure. Uncontrolled inflammation response results in glomerular, tubular, and interstitial damage. This process can cause or contribute significantly to acute kidney injury and chronic kidney disease. The consequence of CKD is end stage kidney disease (ESKD) with Malnutrition-Inflammation-Atherosclerosis (MIA) syndrome and renal anemia.

Keywords: Chronic kidney disease, inflammation, immunity, Malnutrition-Inflammation-Atherosclerosis syndrome, fibroblast

INTRODUCTION

The chronic kidney disease (CKD) is a serious health challenge within every community, with a rising prevalence in recent years, and the progression of this disease is closely related to high mortality as well as morbidity rates. Numerous risks are related to the occurrence and progression of CKD including hypertension, obesity, and diabetes mellitus. Furthermore, there are several evidences about the pathophysiology role of inflammatory response in CKD. Inflammation is a physiological response to different external stimulations to a host cell, including different information, physical-chemical imbalance, antigen challenge, and trauma.[1] Therefore, inflammatory response requires proper regulation, as excess or inadequate is directly related to morbidity and mortality. Meanwhile, previous research showed the negative relations between inflammation mediator circulations and stages of the disease. In CKD patients, inflammation is regarded as an independent mortality predictor.[2] Therefore, inflammatory-immune response modulation is a possible target of CKD treatment.

PATHOGENESIS OF CHRONIC KIDNEY DISEASE

The pathway of CKD pathogenesis is indicated by progressive glomerulus fibrosis and/or tubulointerstitial, peritubular capillary damage due to hypoxia, and nephron function loss caused by glomerulus sclerosis and tubular atrophy, in addition to the main trigger mechanism. Furthermore, increase in inflammation is speculated to be significant during this pathophysiological process.[3] Inflammation is commonly considered as an organism's response to injury, or any incident leading to damage in body cells or tissues. This reaction usually occurs on tissues mediated by substances produced by the damaged as well as the immune cells around the wound.[4] Meanwhile, inflammatory response due to body tissue damage from immune system exacerbation tends to facilitate the disease's occurrence and progress. High inflammatory

response causes loss of peripheral tolerance on that tissue component. This becomes antigenic and exhibits characteristic of local inflammation, a continuous immunology process until the tissue damage ends. Therefore, early activation helps inflammation mediator work on target cells in any part of the body, and cause different morbidity processes, as observed in CKD.[5]

The kidney tissue particularly undergoes inflammation in the kidney damage mechanism for diseases with several etiologies. For instance, in glomerular disease, the disease progression sequence believed to occur is persistent glomerulus injury, leading to capillary hypertension, with increase in glomerulus filtration and protein passage into tubular fluid. Glomerular proteinuria leads to a rise in in angiotensin II. This causes the inflammation mediators (cytokine and chemokine), to be released and induce kidney interstitial formation from mononuclear cells, while macrophage and T lymphocytes replace any premature neutrophil recruitment. The process releases immune response, and produces interstitial nephritis. Also, the response of tubular cells in the inflammatory process with membrane basal damage and mesenchyme epithelial cells transition causes fibroblast formation. These are probably fibroblast growth factor 23 (FGF23), and produce collagen, leading to damage on renal blood vessel and tubules.[6,7]

In addition to glomerulopathy and autoimmune condition, the inflammatory role is depicted by congenital malfunction from urinary canal, as seen in nephropathy obstruction. The pathophysiology mechanism of CKD progress in this obstruction are increasing diameter as well as proliferation of tubular cells and the obstructed kidney. Meanwhile, the mechanical stretching from tubular cells due to obstruction causes the cells to inflame and release cytokine and chemokine to the kidney tissue, as well as tubular cells apoptosis, followed by interstitial compartment, mesenchyme epithelium transition from tubular cells and interstitial cells. This leads to fibroblast formation and proliferation, as well as the activation of inflammation cells, and results in collagen synthesis with matrix cell accumulation, leading to renal fibrosis.[8] Sclerostin and FGF23 are significant for this synthesis.[7]

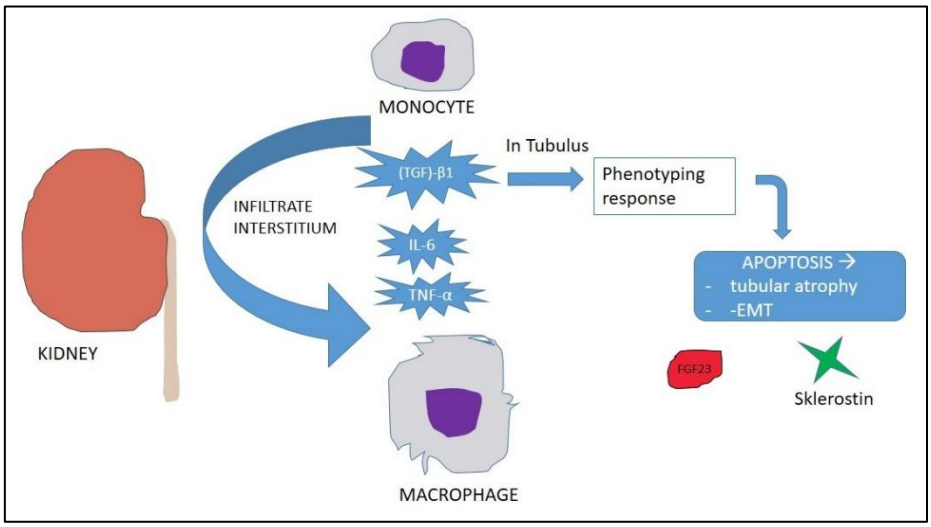

Fig.1:The role of fibroblast induces fibrosis in kidney.

TGF = transforming growth factor; IL-6 = interleukin 6; TNF- = tumor necrosis factor; FGF23 = fibroblast growth factor 23; EMT = epithelial-to-mesenchymal transition.

The obstructive nephropathy with renal cellular interactions produces fibrosis in renal interstitial. This is because monocytes are "classically" activated to macrophages after infiltrating the interstitium. The process releases cytokines, including transforming growth factor (TGF)-β1, interleukin 6 (IL-6) and tumor necrosis factor α (TNF-α). TGF-β1 in turn, induces a phenotypic response in tubular epithelial cells. Consequently, the cells undergo either apoptosis (leading to tubular atrophy) or epithelial-mesenchymal transition (EMT), fibroblast growth factor especially fibroblast growth factor 23 (FGF23), scelerostin, and become fibroblasts, then move to the interstitium.[7] (Figure 1). Meanwhile, angiotensin II (ANG II), released by monocyte activation, incites the production of nuclear factor kappa B (NFκB), leading to increase in macrophages recruitment as well as reactive oxygen species (ROS) production, and this aggravates renal tubular injury. Conversely, alternatively activated macrophages are able to enhance tubular cell survival and proliferation, and endothelial cells are able to undergo endothelial-mesenchymal transition (EndMT) or apoptosis, leading to capillary loss, hypoxia by hypoxia-inducible factor 1-alpha

(HIF-1-α), and secondary renal ischemia. Furthermore, infiltrating hematopoietic stem cells and resident pericytes also tend to differentiate into fibroblasts. Cytokines, including TGF-β1, IL-6, TNF-α, NFκB, and FGF23 from macrophages or other cells are able to stimulate fibroblasts to carry out stress fiber synthesis and further differentiate to turn into myofibroblasts. These myofibroblasts are contractile, and intensify extracellular matrix (ECM) deposition, thus, causing progressive interstitial fibrosis. This augmentation is due to a reduction in the degradation of ECM, and is mediated by tissue-type plasminogen activator (tPA) and plasminogen activator inhibitor-1 (PAI-1).[9,10] (Figure 2)

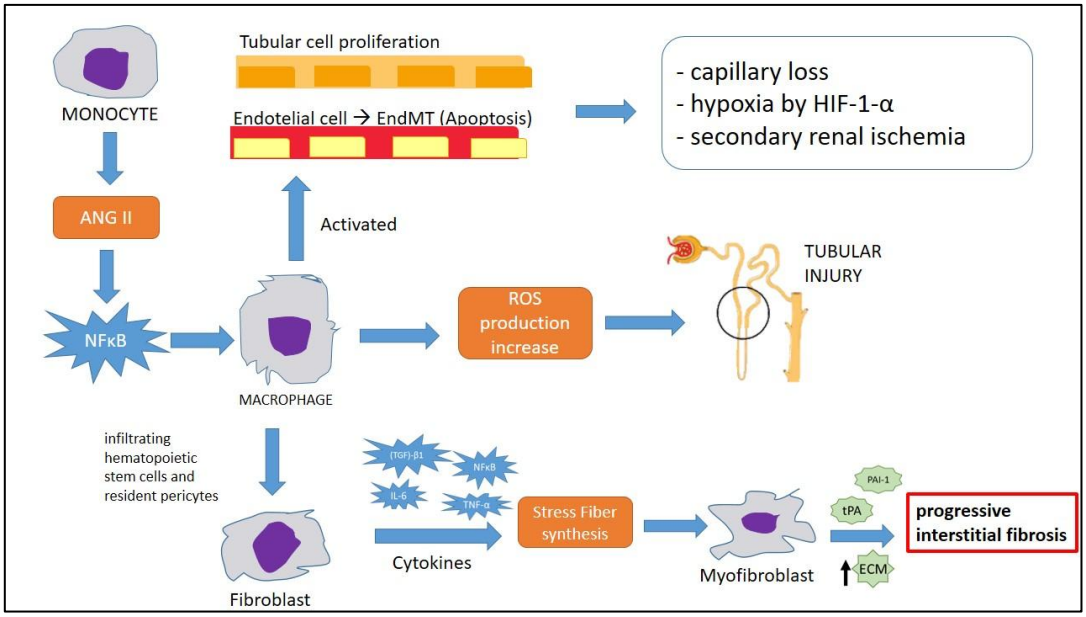

Fig.2: Renal cellular interactions to make progressive interstitial fibrosis in kidney.

EndMT = endothelial-mesenchymal transition; ANG II = angiotensin II; NFκB = nuclear factor kappa B; ROS = reactive oxygen species; TGF = transforming growth factor; IL-6 = interleukin 6; TNF-α = tumor necrosis factor α; HIF-1-α = hypoxia-inducible factor 1-alpha; tPA = tissue-type plasminogen activator; PAI-1 = plasminogen activator inhibitor-1; ECM = extracellular matrix.

The vicious cycle in chronic kidney disease (CKD) progression comprises tubulointerstitial hypoxia (HIF-1-α), inflammation (IL-1, IL-6, IL-23, and TNF-α), and oxidative stress (ROS).[10,11] Decreasing peritubular capillary (PTC) blood flow and subsequent tubulointerstitial hypoxia is due glomerular injury. Also, tubular injury is caused by hypoxia and proteinuria, and this in turn initiates cytokine as well as chemokine production and promotes the infiltration of inflammatory cells into the tubulointerstitium. This infiltration is also triggered by damaged PTC. Meanwhile, inflammation, hypoxia, and oxidative stress foster trans-differentiation in resident fibroblasts, pericytes, or renal erythropoietin-producing cells to become ECM-producing myofibroblasts, and the direct interactions between myofibroblasts and injured tubular cells are significant. Also, fibrosis causes further impairment in local oxygenation.

INNATE IMMUNITY AND KIDNEY DISEASE

The most significant innate immunity components involved in the progress of kidney disease are complement system, toll like receptor (TLR), dendritic cell, macrophage, natural killer cells (NK cells), and inflammatory cytokines, while the early components of innate immune response are serum surface protein and cells. TLR is a group of proteins on a cell's surface serving as the pattern introduction receptor. These proteins often tie microbe pathogen and initiate inflammatory response. In addition, TLR has been involved in the process of acute kidney injury (AKI) and chronic kidney disease (CKD). Macrophages are phagocytes obtained from monocytes, found in peripheral tissue, and often classified in subpopulations as M1 or M2. These cells are crucial in inflammatory mediation and immunity modulation, and are usually activated by immune complex related to the complementary or adaptive immune cells system (T lymphocytes and cytokine). In kidney disease, macrophage activation commonly transpires secondarily to complete the activation or T cell effector performed by nonspecific antigen in the kidney. Therefore, macrophage is possibly not the early trigger of kidney disease.

However, AKI and CKD (including glomerulonephritis) mediated by autoimmune are associated with increase in kidney macrophage.[12] The pro-inflammation of M1 is related to kidney disease and activated classically by inflammatory cytokine, including interferon gamma (IFN-γ) or TNF-α, and this is passed down from innate cells or adaptive immune system. The activated macrophage classically releases inflammatory cytokine, increase oxidative stress, and progresses renal fibrosis. In addition, the activated cells take up residual cellular waste, and are able to increase renal infiltration in a bid to balance the wound healing process. Inflammation and injury are mediated by the releasing macrophage inflammation cytokines including IL-1, IL-6, IL-23, and the generating reactive nitrogen/oxygen species, has been involved in kidney function disorder.[13]

The NK cell causes possible macrophage activation through IFN-γ release. This is automatically carried out by the cells without Major Histocompatibility Complex type 1 (MHC-I). The nonspecific response to foreign pathogens makes NK cell a significant mediator of innate immunity. In the kidney, this cell is generally associated with AKI, promotes apoptosis to tubular epithelium cell, and undergoes depletion to protect the kidney from reperfusion ischemic damage.[14]

Meanwhile, in CKD caused by autoimmune, the role of NK cell in kidney damage is currently unclear. The presentation of antigen by dendritic is the key step in adaptive immunity activation, possibly induces the production of NK cell cytokine (IFN-γ) and as a result, facilitates kidney disease progression. Furthermore, NK cells destroy autoimmune disease causing autoreactive T cells, and are therefore able to provide protection from CKD by managing the body's adaptive immune system function. The ability of NK cells to respond to nonspecific stimulation and recognize autoreactive T cell show the cells are located at the intersection between adaptive and innate immune responses.[15,16]

ADAPTIVE IMMUNITY CELLS AND KIDNEY DISEASE

The adaptive immunity system function is mostly regulated by B lymphocytes (humoral immunity/mediated-antibody) and T lymphocytes (immunity mediated by cells). B lymphocytes produce kidney disease facilitating autoantibody, including systemic lupus eritematosus (SLE), immunoglobulin nephropathy A (IgA), and Goodpasture syndrome. The two main types of T cells are the cells mediated by adaptive immunity system, T cytotoxic /$CD8^+$ T (cytotoxic T-cell [T_C] / $CD8^+$ T-cell) and the helper $CD4^+$ T (helper T-cell [T_H] / $CD4^+$ T-cell).

Furthermore, the $CD8^+$ T-cell is analogous with NK cell from innate immunity system because of the role in destroying infected cells. However, the two differ because $CD8^+$ T is unable to recognize the specific antigen on MHC-I molecule (NK cell recognizes the cell without MHC-I). The $CD8^+$ T-cell has complex roles, mainly in CKD such as lupus nephritis, and tends to be activated by specific kidney auto-antigen, leading to local damage while playing a role in kidney disease and swelling. This way, the activated $CD8^+$ T-cell tend to discharge additional kidney specific auto-antigens and promote the vicious circle, leading to further activation, and consequently, more kidney damages. Therefore, with this increase in the activated cell in the SLE patient's kidney, there is an equivalent rise in the population of $CD8^+$ T with injury protection potential, partly by suppressing pathogenic $CD4^+$ T.[17] The $CD4^+$ T-cell represents the other main players in immunity mediated by cells and is activated by inflammatory cytokine and antigen presenting cell (APC). In addition, the cells are classified further into subparts based on the main functions or the cytokine type produced, and these include T_H1, T_H2, T_H17, and T regulatory (T_{reg}). T_H is indicated by inflammatory cytokine production, including IFN-γ, IL-2, lymphotoxin-α, and dan TNF-α. The subset of polarized T_H1 increases macrophage cell activation, while the T_H2 counterpart secretes cytokine (IL-4, IL-5, dan IL-10), and is often called "anti-inflammatory" because of the ability to regulate T_H1 and suppress macrophage activation. However, as a result of consistency with the many complex aspects of body immune system function, cytokine from T_H2 polarization cell has many roles in regulating the immune system. The T_H2 cytokine increases B cell differentiation, resulting in typical autoantibody production, and is able to cause typical autoimmune disorder. These different functions of T_H1 and T_H2 cytokine finally resulted in a model proposed to describe kidney disease because of T_H1 or 2 dominations. For instance, in crescentic glomerulonephritis, the form of acute nephritis rapidly progressing to the end-stage of kidney disease, is often considered to be T_H1 dominated. Conversely, in membranous glomerulonephritis, a kind of chronic nephritis due to immune complex formed as a response to autoantigen from glomerulus basal membrane, is regarded as T_H2 dominated. Therefore, a kidney disease including lupus nephritis, is expected to be related toT_H1 and T_H2 cytokines.[18]

Furthermore, while these two represent the classic model to define immunity diseases, there are two other $CD4^+$ T cells currently known for significance

in inflammation related to kidney disease. The T_H17 ($CD4^+ROR\gamma^+$ T-cell) is relatively new, and produces IL-17, IL-21, and dan IL-22 cytokine. This cell is also able to escalate partial kidney inflammation by increasing TNF-α expression and regulation on the chemokine responsible for immunity cell invasion to the kidney. Currently, the T_H17 cell is admittedly an important mediator of autoimmune nephritis related inflammation and tissue injury. Prior research showed stimulating nephrotoxic nephritis by injecting mice with sheep serum causes kidney damage related with IL-17-producing T-cells. Repeating this experiment with knockout (KO) IL-17 mouse causes nephritis progress to be blunt.[19] In addition, the infiltration of these cells increases in MRL-Fas^{lpr} with SLE model tubules interstitial room. A similar relation is shown between IL-17 and kidney disease related to autoimmune, by breaking down TNF 1 (TNFR1) and TNF 2 (TNFR2) receptors in 2328 SLE Mix New Zealand mice. These receptors accelerate kidney injury in this mouse model, with regard to T_H17 phenotype activation. Generally, this research shows the significant role of T_H17 cell in CKD pathogenesis.[20]

Finally, there is a subpart of T cells regulator (T_{reg}), known as $CD4^+CD25^+FoxP3^+$ T_{reg} cell. The T_{reg} cell suppresses adaptive immune system function and increases self-tolerance in a bid to provide protection for autoimmune disease. This immunomodulatory action occurs through cytokine release, including converting cytokine-inhibiting TGF-β dan IL-10. The depletion and/or dysfunction of T cells regulator causes autoimmune disease as well as inflammation. Meanwhile, the addition of T_{reg} cell is able to postpone the occurrence of kidney damage and inflammation related to autoimmune nephritis and this confirms the cell's protective role in kidney injury. However, the detailed mechanism of T_{reg} in the model of innate and adaptive immunity as components of immune system and inflammatory role in kidney disease pathogen is currently under investigation.[21,22]

CYTOKINE AND CHEMOKINE IN KIDNEY DISEASE

Cytokine is a soluble low molecular protein secreted by cells including leukocytes, mainly in reaction to stimulation by antigenes, and serves as a messenger from body immune system. The cytokine mostly synthesized by mononuclear phagocyte is referred to as monokine, while the counterpart mostly synthesized by lymphocyte is called lymphokine. In addition, the cytokine working toward other leukocytes is referred to as interleukin (IL), and is involved in antigen response as well as presentation, mainly by T_H lymphocyte. Meanwhile, the counterpart with the role of basic traffic control and leukocyte inflammation through chemotaxis, is called chemokine, and this is an important facilitator of mobilization, the basic characteristic of body immune cells. Also, chemokine has proangiogenic effect and is able to increase leukocyte degranulation. This way, immunity response ultimately consists of a combination of biological functions.[23]

Furthermore, there are clinical and experimental evidences behind the roles of cytokine and chemokine in various kidney injury mechanisms. In kidney tissue, cytokine induces local proliferation in tubular cells and interstitial, extracellular matrix generates, procoagulant endothelial activity, reactive oxygen species formation, and rise in adhesive molecule expression as well as biologically active lipids. The release of cytokine is also linked to hemodynamic and local effect of renin-angiotensin system (RAS) activation.[23-25]

Inflammatory cytokine has a pivotal role as mediator of immunity function and initiator of kidney injury, whether in acute or chronic kidney disease, and regardless of innate or adaptive immunity. In addition, cytokine also serves as the immunomodulator and possibly inhibits the progress of kidney disease. For instance, T_H1 IFN-γ cytokine has potential multiple roles in kidney disease pathogenesis, capable of enforcing and limiting the disease progress. Numerous studies explained the direct transfer of IL-12 secretion cell under MRL-Fas^{lpr} kidney capsule leprosy nephritis mode leads to kidney injury. However, the kidney is protected in cases where the experiment is performed on a MRL-Fas^{lpr} mouse without IFN-γ receptor. Conversely, IFN-γ receptors helps to reduce the progress of kidney injury due to progression factor exuded by macrophage on the kidney.[26]

INFLAMMATORY EFFECT ON CKD

The severe effects of CKD include metabolic complications (hypertension, anemia, malnutrition, bone and minerals abnormalities, and other related ailments) as well a rise in the risk of cardiovascular disease, 100 times higher compared to the general population. This accounted for about half of the total death of renal replacement therapy (RRT) patients in North America are. However, this value is slightly lower in Hong Kong (30-40%), and is parallel with mortality because of infection.[27] Epidemiologically, inflammation has been identified as the main cause of vascular atherosclerotic disease and heart valve calcification, the risk factors in CKD. The rise in inflammatory proteins, including plasma C-reactive protein (CRP) and serum amyloid A (SAA), is a strong predictor from all causes of mortality and cardiovascular mortality in end stage

kidney disease (ESKD) patients. Inflammation involves complex interactions between immunity cells, dissolved proteins (cytokine, chemokine, adhesion, and co-stimulatory molecule), and fibroblast, possibly fibroblast growth factor 23 (FGF23) occurring on the affected tissue as a response to infection, trauma, ischemia, autoimmune injury, or fibrosis.[28,29]

Meanwhile, a frequently occurring complication in CKD is Malnutrition, Inflammation, and Atherosclerosis (MIA) syndrome. Malnutrition is common to about 76% of ESKD patients, as well as clinical weight loss, energy depletion (adipose tissue), somatic protein loss (muscle mass), accompanied by reduction in plasma albumin, retinol binding protein, transferrin, pre-albumin, and concentration of A-I apolipoprotein (apo).[30] The degree of malnutrition anthropometrically and serologically, is not correctible with oral nutrition supplementation, and is tied to unfavorable results. Inflammation has a more crucial role in atherosclerosis initiation and progression, and is considered the main non-traditional hazard factor while accelerating intima thickening and carotid formation in dialysis patients. The rise in plasma CRP concentration (>5 mg/L) is related to higher atherosclerotic vascular disease and also tightly connected to heart hypertrophy or dilation. Other inflammatory proteins increasing during CKD and cause vascular disease include fibrinogen and lipoprotein, with thrombogenic characteristic in addition to atherogens. During inflammation, A-I apo lever synthesis, the main structural protein of high-density lipoprotein (HDL) decreases. As a result, positive acute phase SAA protein replaces A-I apo on HDL, and this alters the structure and function of spreading HDL. The particles therefore become more attached to the arterial damage-causing endothelial surface vascular, and lower the protection given to the LDL oxidation-facilitating atherogenesis .[31]

Furthermore, dialysis patients both peritoneal dialysis (PD) and hemodialysis (HD) with malnutrition often experience inflammation characterized by elevated plasma CRP levels, and imbalance of pro and anti-inflammatory cytokines. The inflammation and malnutrition markers are able to predict mortality in CKD patients on dialysis, especially in cases of morbidity caused by cardiovascular disease and up 20% of the initial mortality of patients with PD. Also, there is a strong association between these two complications as well as atherosclerosis in CKD patients, often referred to as MIA (malnutrition, inflammation and atherosclerosis) syndrome. Therefore, early recognition of the MIA syndrome is crucial for identifying patients with high risk factors.

The C-reactive protein (CRP) is able to independently predict atherosclerotic plaque in the carotid arteries and also serves as a sensitive marker of all cases of cardiovascular and general mortality in CKD. Several infections including C. pneumoniae, peritonitis infections, comorbid conditions such as diabetes, congestive heart failure and advanced glycation end products (AGE) accumulation, biocompatibility of dialysis fluids and exposure to dialysis fluids with endotoxins, are factors contributing to inflammation. In addition, oxidative stress with oxygen free radicals, decrease in antioxidant (vitamins A, C, E, glutathione and selenium) levels, concomitant diseases including SLE, acquired immunodeficiency syndrome (AIDS), as well as genetic (racial) predisposition increasing the production of IL-6 and CRP genes. For instance, Caucasians are predisposed to inflammation.[32,33,34]

In uremic malnutrition, there is a loss of somatic protein and visceral protein (serum and pre albumin) reserves, and this is linked to increase in mortality. The presence of serum creatinine < 9 mg/dl and serum albumin < 3.2 mg/dl, increase the incidence of mortality by 2 and 5 times, respectively. Several studies have shown two types of malnutrition in CKD. The first is associated with low nutritional intake in the absence of inflammation, while the second is associated with the presence of inflammation. Also, there is a strong association between hypoalbuminemia, malnutrition, and inflammation.

Reduction in protein intake occurs as a result of anorexia, nausea and vomiting, abdominal pain, increase in catabolism (due to metabolic acidosis and insulin resistance), resting energy expenditure (REE), as well as glucose absorption leading to hormonal disorders. Meanwhile, higher free radical production and decreased antioxidant levels will lead to atherogenesis and endothelial dysfunction. According to the multivariate analysis, CRP and albumin are accurate predictors of mortality. Serum albumin is the main antioxidant, therefore hypoalbuminemia tends to cause oxidative stress and atherogenesis.

Furthermore, atherosclerosis and coronary artery calcification are very common to CKD patients, and chronic inflammation is a major contributing factor. Proinflammatory cytokines such as IL-6, TNF-α and acute phase reactants (CRP and fibrinogen), are atherogenic and thrombogenic.[35] Hence, oxidative stress, AGE, hyperphosphatemia and increased calcium-phosphorus production accelerate the occurrence of atherosclerosis. Serum IgA levels are also able to predict the progression of atherosclerosis through interactions with endothelial receptors, in the presence of C. pneumonia and some other infectious conditions.

Anemia is the main complication in stage 2-5 CKD influencing over 50% of ESKD patients before treatment. This condition is due to chronic inflammation speeding up erythrocytes destruction, hematocrit, and hemoglobin decrease, iron decrease, transferrin and transferrin receptor, hyperferritinemia, and erythropoietin decrease.[36] Anemia impairs cognitive functions, heart function, exercise capacities as well as other life qualities, and is connected to the rise in cardiovascular disease and all death causes in CKD patients.

During the inflammation process in CKD, IL-1β, a pro-inflammatory cytokine, causes functional iron deficiency by increasing the expression of Cyp27b1 (Cytochrome P450 Family 27 Subfamily B Member 1) in the kidneys and ultimately, leading to a rise in the level of FGF23. Meanwhile, hepcidin, a functional mediator of iron deficiency, is produced by the liver in response to inflammation and results in increased iron sequestration as well as decreased intestinal absorption. In mice treated with exogenous hepcidin, an increase in the serum levels of cFGF23 and expression of FGF23 mRNA, were observed.[37]

CONCLUSION

The contributions of body immune system and inflammation to kidney disease and other ailments are now better understood. Furthermore, inflammatory mediators possibly influence kidney hemodynamic, sodium and blood pressure regulation and water homeostasis. Meanwhile, uncontrolled inflammation results in tubular, glomerular, and interstitial damage. Therefore, this pathological process is significant to acute and chronic kidney diseases. Inflammation related to cardiovascular disease and diabetes cause significant kidney pathological progress, hence, the current therapeutic approach targets the body immune system and inflammatory response regulation.

In addition, the appearance of genetically manipulated mice, bone marrow transplant study, and therapeutic approaches based on antibodies, have contributed to the roles of immune system and inflammatory response in kidney disease. Several significant studies about inflammatory mediators contributing kidney pathology in hypertension, diabetes, and nephrotic as well as nephritis syndromes, have been performed, however, numerous factors require further research. Immunology contributions including cytokine, T cell, B cell, and surface molecule on inflammatory cells toward kidney function, give new insight on kidney disease progression, thus, extensive investigations ought to be carried out.

CONFLICT OF INTEREST

The authors have no conflicts of interest.

ACKNOWLEDGEMENTS

This work is supported by the faculty of medicine, Universitas Padjadjaran, Bandung, Indonesia. We thank our colleagues for their excellent contributions.

FUNDING

This work was supported by the Academic Leadership Grant (ALG) Universitas Padjadjaran (contract no.2476/UN6.C/LT/2018).

REFERENCES

1. Suliman ME, Stenvinkel P. Contribution of inflammation to vascular disease in chronic kidney disease patients. Saudi J Kidney Dis Transpl. 2008; 19(3): 329-345.
2. Oberg BP, McMenamin E, Lucas FL, et al. Increased prevalence of oxidant stress and inflammation in patients with moderate to severe chronic kidney disease. Kidney Int. 2004; 65(3): 1009-1016.
3. Eddy AA. Progression in chronic kidney disease. Adv Chronic Kidney Dis. 2005; 12(4): 3533-65.
4. El Nahas AM. The global challenge of chronic kidney disease. Kidney Int. 2005; 68(6): 2918-2929.
5. Gerard C, Rollins BJ. Chemokines and disease. Nat Immunol. 2001; 2(2): 108-115.
6. El Nahas AM, Bello AK. Chronic kidney disease: the global challenge. Lancet. 2005; 365(9456): 331-340.
7. Rudiansyah M, Lubis L, Bandiara R, et al. The Correlation between Fibroblast Growth Factor 23 (FGF23) and Iron Profile in Chronic Kidney Disease Patients on Dialysis with Anemia. Syst Rev Pharm. 2020; 11(6): 780-784.
8. Chevalier RL, Thornhill BA, Forbes MS, Kiley SC. Mechanisms of renal injury and progression of renal disease in congenital obstructive nephropathy. Pediatr Nephrol. 2010; 25(4): 687-697.
9. Chevalier RL, Forbes MS, Thornhill BA. Ureteral obstruction as a model of renal interstitial fibrosis and obstructive nephropathy. Kidney Int. 2009; 75(11): 1145-1152.
10. Valentin D, Aline M, Tamara I, et al. Inflammation and functional iron deficiency regulate fibroblast growth factor 23 production. Kidney Int. 2016; 89(1): 135-146. https://doi.org/10.1038/ki.2015.290.
11. Yamaguchi J, Tanaka T, Nangaku M. Recent advances in understanding of chronic kidney disease [version 1; peer review: 3 approved]. F1000Research. 2015; 4(F1000 Faculty Rev): 1212. https://doi.org/10.12688/f1000research.6970.1

12. Hisada Y, Sugaya T, Yamanouchi M, et al. Angiotensin II plays a pathogenic role in immune-mediated renal injury in mice. J Clin Invest. 1999; 103(5): 627-635.
13. Ghee JY, Han DH, Song HK, et al. The role of macrophage in the pathogenesis of chronic cyclosporine-induced nephropathy. Nephrol Dial Transplant. 2008; 23(12): 4061-4069.
14. Zhang ZX, Wang S, Huang X, et al. NK cells induce apoptosis in tubular epithelial cells and contribute to renal ischemia-reperfusion injury. J Immunol. 2008; 181(11): 7489-7498.
15. Smeltz RB, Wolf NA, Swanborg RH. Inhibition of autoimmune T cell responses in the DA rat by bone marrow-derived NK cells in vitro: Implications for autoimmunity. J Immunol. 1999; 163(3): 1390-1397.
16. Flodström M, Shi FD, Sarvetnick N, Ljunggren HG. The natural killer cell – friend or foe in autoimmune disease? Scand J Immunol. 2002; 55(5): 432-441.
17. Panzer U, Kurts C. T cell cross-talk with kidney dendritic cells in glomerulonephritis. J Mol Med. 2010; 88(1): 19-26.
18. Hirayama K, Ebihara I, Yamamoto S, et al. Predominance of type-2 immune response in idiopathic membranous nephropathy. Cytoplasmic cytokine analysis. Nephron. 2002; 91(2): 255-261.
19. Paust HJ, Turner JE, Steinmetz OM, et al. The IL-23/Th17 axis contributes to renal injury in experimental glomerulonephritis. J Am Soc Nephrol. 2009; 20(5): 969-979.
20. Jacob N, Yang H, Pricop L, et al. Accelerated pathological and clinical nephritis in systemic lupus erythematosus-prone New Zealand Mixed 2328 mice doubly deficient in TNF receptor I and TNF receptor 2 via a Th17-associated pathway. J Immunol. 2009; 182(4): 2532-2541.
21. Schöndorf T, Musholt PB, Hohberg C, et al. The fixed combination of pioglitazone and metformin improves biomarkers of platelet function and chronic inflammation in type 2 diabetes patients: results from the PIOfix study. J Diabetes Sci Technol. 2011; 5(2): 426-432.
22. Imig JD, Ryan MJ. Immune and inflammatory role in renal disease. Compr Physiol. 2013; 3(2): 957-976.
23. Mackay CR. Chemokines: immunology's high impact factors. Nat Immunol. 2001; 2(2): 95-101.
24. Rudiansyah M, Nur'amin HW, Nugrahaningsih DAA, Bandiara R, Roesli RMA. COVID-19: Drug development and kidney related problems. Syst Rev Pharm. 2020;11(7):106-112.
25. Rudiansyah M, Nur'amin HW, Lubis L, Bandiara R, Roesli RMA, Rachmadi D. COVID-19 and kidney diseases in Indonesia. Syst Rev Pharm. 2020; 11(7): 435-442.
26. Schwarting A, Moore K, Wada T, Tesch G, Yoon HJ, Kelley VR. IFN-□ limits macrophage expansion in MRL-Fas^{lpr} autoimmune interstitial nephritis: A negative regulatory pathway. J Immunol. 1998; 160(8): 4074-4081.
27. Wang AYM, Lam CWK, Yu CM, et al. Troponin T, left ventricular mass, and function are excellent predictors of cardiovascular congestion in peritoneal dialysis. Kidney Int. 2006; 70(3): 444-452.
28. Pickup JC. Inflammatory markers and type 2 diabetes. Diabetes Technol Ther. 2006; 8(1): 1-6.
29. Rudiansyah M, Lubis L, Bandiara R, et al. Java Barb Fish Gallbladder–Induced Acute Kidney Injury and Ischemic Acute Hepatic Failure. Kidney Int Reports. 2020; 5(5): 751-753.
30. Stenvinkel P, Heimbürger O, Lindholm B, Kaysen GA, Bergström J. Are there two types of malnutrition in chronic renal failure? Evidence for relationship between malnutrition, inflammation and atherosclerosis (MIA syndrome). Nephrol Dial Transplant. 2000; 15(7): 953-960.
31. Wang AYM, Ho SSY, Liu EKH, et al. Differential association of traditional and non-traditional risk factors with carotid-intima-thickening and plaque in peritoneal dialysis patients. Am J Nephrol. 2007; 27(5):458-465.
32. Ronco C, Dell'Aquila,R. Peritoneal Dialysis A Clinical Update. Ronco C, editor. Switzerland: Karger AG; 2006.
33. Pecoits-Filho R, Bárány P, Lindholm B, Heimbürger O, Stenvinkel P. Interleukin-6 is an independent predictor of mortality in patients starting dialysis treatment. Nephrology Dialysis Transplantation. 2002; 17(9): 1684-1688.
34. Rudiansyah M, Bandiara R, Supriyadi R, Lubis L, Kurniaatmaja ER, Nur'amin HW, Roesli RMA. The severe varicella zoster infection with kidney transplant patient using immunosuppressant. International journal of pharmaceutical research. 2021; 13(1): 852-857
35. Kang D-H, Kang EW, Choi SR, Yoon S-Y, Han D-S. Nutritional problems of Asian peritoneal dialysis patients. Peritoneal dialysis international. 2003; 23(Supplement 2): S58-S64.
36. Wiecek A, Covic A, Locatelli F, Macdougall IC; ORAMA study group. Renal anemia: comparing current Eastern and Western European management practice (ORAMA). Ren Fail. 2008; 30(3): 267-276.
37. David V, Martin A, Isakova T, et al. Inflammation and functional iron deficiency regulate fibroblast growth factor 23 production. Kidney International. 2016; 89(1); 135–146.