Review Article

Immunosenescence, gut dysbiosis, and chronic kidney disease: Interplay and implications for clinical management

Tao Han Lee [a], Jia-Jin Chen [b], Chao-Yi Wu [c], Ting-Yun Lin [d], Szu-Chun Hung [d,**], Huang-Yu Yang [b,e,*]

[a] Nephrology Department, Chansn Hospital, Taoyuan, Taiwan
[b] Kidney Research Center, Nephrology Department, Chang Gung Memorial Hospital in Linkou, Chang Gung University College of Medicine, Taoyuan, Taiwan
[c] Division of Allergy, Asthma, And Rheumatology, Department of Pediatrics, Chang Gung Memorial Hospital, College of Medicine, Chang Gung University, Taoyuan, Taiwan
[d] Division of Nephrology, Taipei Buddhist Tzu Chi General Hospital, Buddhist Tzu Chi University, Taipei, Taiwan
[e] Department of Health Policy and Management, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

ARTICLE INFO

ABSTRACT

Immunosenescence refers to the immune system changes observed in individuals over 50 years old, characterized by diminished immune response and chronic inflammation. Recent investigations have highlighted similar immune alterations in patients with reduced kidney function. The immune system and kidney function have been found to be closely interconnected. Studies have shown that as kidney function declines, both innate and adaptive immunity are affected. Chronic kidney disease (CKD) patients exhibit decreased levels of naive and regular T cells, as well as naive and memory B cells, while memory T cell counts increase. Furthermore, research suggests that CKD and end-stage kidney disease (ESKD) patients experience early thymic dysfunction and heightened homeostatic proliferation of naive T cells. In addition to reduced thymic T cell production, CKD patients display shorter telomeres in both CD4+ and CD8+ T cells.

Declining kidney function induces uremic conditions, which alter the intestinal metabolic environment and promote pathogen overgrowth while reducing diversity. This dysbiosis-driven imbalance in the gut microbiota can result in elevated production of uremic toxins, which, in turn, enter the systemic circulation due to compromised gut barrier function under uremic conditions. The accumulation of gut-derived uremic toxins exacerbates local and systemic kidney inflammation. Immune-mediated kidney damage occurs due to the activation of immune cells in the intestine as a consequence of dysbiosis, leading to the production of cytokines and soluble urokinase-type plasminogen activator receptor (suPAR), thereby contributing to kidney inflammation.

In this review, we delve into the fundamental mechanisms of immunosenescence in CKD, encompassing alterations in adaptive immunity, gut dysbiosis, and an overview of the clinical findings pertaining to immunosenescence.

At a glance commentary

Scientific background on the subject

Immunosenescence, which becomes apparent in individuals aged 50 and above, involves the manifestation of diminished immune responses and chronic inflammation. This phenomenon is also observed in patients with reduced kidney function. The growing recognition of the interconnectedness between immunity and kidney health underscores the importance of this field.

What this study adds to the field

In the present review, we delve into the fundamental mechanisms

---

underlying immunosenescence within chronic kidney disease (CKD). This examination comprehensively explores alterations in adaptive immunity, gut dysbiosis, and clinical observations. By unveiling the intricate interplay between immune decline and kidney function, this review sheds light on the complex relationships. These insights pave the way for potential therapeutic strategies targeting both immune response and kidney inflammation.

Introduction

Immunosenescence usually refers to the phenomenon of defective immune response and chronic inflammation caused by changes in the immune system in healthy individuals aged 50 years or older. As individuals age, the process of autophagy in immune cells declines, impeding the breakdown of dysfunctional mitochondria. This results in the accumulation of reactive oxygen species and DNA damage. These physiological changes, along with aging, impair vaccine responses and increase susceptibility to infection, autoimmunity, and cancer [1].

Chronic kidney disease (CKD) is typically defined as kidney damage or a glomerular filtration rate (GFR) of <60 mL/min/1.73 m^2 or proteinuria/structural change for 3 months or more [2]. Previous studies have shown that as kidney function declines, CKD patients are predisposed to a higher cardiovascular risk, increased susceptibility to infection and certain types of cancers, and reduced response to immunization [3,4]. According to a study based on the US Renal Data System, from 2001 to 2010, the mortality risk due to sepsis is approximately 250-fold higher among end stage kidney disease (ESKD, also known as kidney failure) patients than in the general population [5]. An international collaborative study revealed a significantly increased risk of certain cancers in patients under dialysis. This study reported that ESKD patients had a 1.6–4 standardized incidence ratio (SIR) of cervical cancer, which is usually secondary to papillomavirus, and a 1.2–1.5 SIR of liver cancer, which may be associated with hepatitis B and C viruses [6].

Currently, investigators have revealed the close and interactive connection between the immune system and kidney function, which is independent of the underlying disease of kidney insufficiency and may be one reason why patients with kidney insufficiency are more fragile. Previous studies have grouped CKD patients into the "inflamm-aging" condition, which shifts lymphocytes toward a senescent and exhausted phenotype, similar to the aging process [7,8]. Immunological aging in patients with ESKD is accelerated and increased by 20 years compared with age-matched healthy individuals [1]. Furthermore, kidney insufficiency alters the environment inside the intestinal lumen, leading to gut dysbiosis, which further affects intestinal immunity. Moreover, several factors have been observed to be associated with heightened systemic inflammation during the dialysis procedure. These include the transmembrane passage of bacterial lipopolysaccharide (LPS) from contaminated dialysate into the blood component [9], activation of mononuclear cells and the subsequent increase in production of proinflammatory cytokines upon contact with the dialysis membrane [10], activation of the complement system upon blood–membrane interaction [11], and an increase in reactive oxygen species (ROS) and depletion of antioxidants during hemodialysis [12]. In this review, we discuss the key mechanisms of immunosenescence in CKD, from changes in adaptive immunity to gut dysbiosis, and summarize the clinical results of immunosenescence.

Altered innate and adaptive immunity in chronic kidney disease

Change of innate immunity in chronic kidney disease

The innate immunity is characterized by non-specific recognition of self and non-self stimuli through pattern recognition receptors (PRRs). These receptors are present in various myeloid cells, which serve as the first line of defense against pathogens. Activation of PRRs triggers immune cell activation, complement system activation, and coagulation system activation [13,14]. Multiple studies have reported increased expression of PRRs in different kidney diseases. For instance, TLR4 (TLR, toll-like receptor) expression is increased in lupus nephritis [15], anti-neutrophil cytoplasmic antibody-associated vasculitis/nephritis [16], sepsis-associated kidney injury [17], ESKD [18], and aging kidney [19]. Xi et al. demonstrated through animal models that several components of innate immunity are overexpressed, including TLR1, 2, 3, 4, 5, 11, as well as heat-shock protein 70 (HSP70) and high mobility group box 1 (HMGB1). It is proposed that TLR upregulation leads to the induction of proinflammatory cytokines, fibrosis, and progression of CKD [19]. According to this investigation, different kidney diseases or aging kidneys can activate innate immunity in the kidney, resulting in the progression of CKD [19].

Kidney disease can lead to increased local innate immunity in the kidney, as well as systemic activation and dysfunction of the innate immune system in various aspects [20]. Patients with ESKD exhibit expansion of the CD14+CD16+ subset in circulating monocytes, along with increased expression and activity of TLR4 in neutrophils and monocytes [18]. The production of pro-inflammatory cytokines tumor necrosis factor (TNF) and interleukin-6 (IL-6) by activated monocytes was also increased [18], which was associated with increased systemic inflammation. However, impaired phagocytic activity against pathogens has been observed in uremic patients [21]. Uremia is also associated with depletion of the plasmacytoid dendritic cell subset, and the hemodialysis procedure significantly impairs the ability to produce tumor necrosis factor-α (TNF-α) in response to LPS [22]. Verkade et al. demonstrated impaired stimulation of allogeneic T-cells by dendritic cells in advanced kidney disease patients [23]. For short, uremia is associated with dysregulation of innate immunity, characterized by upregulation of chemokine/chemokine and ROS production [24], impaired phagocytosis, and impaired stimulation of T cells [20].

Change of adaptive immunity in chronic kidney disease

The adaptive immune system generates immunological memory following an initial response to a specific pathogen, which can lead to an experienced and enhanced response when re-encountering that pathogen in the future. In patients with declining kidney function, nitrogenous compounds and cytokines that are usually cleared by the kidney accumulate in the body, a condition known as uremia. Uremia has a detrimental effect on the quantity and quality of the adaptive immune system [3]. The number of naive T cells, regular T cells, and both naive and memory B cells decrease, while memory T cells increase in number. By analyzing the profile of T cell subsets, Litjens et al. observed a decrease of 50% in naive CD4 T cells (CCR7+CD45RO-) and a corresponding 34% rise in central memory CD4 T cells (CCR7+CD45RO+) among CKD stage 5 patients as compared to healthy individuals. A similar cellular shift was also observed in the group of CD8 T cells, with a reduction in naive CD8 T cells (CCR7+CD45RO-) and an increase in effector memory CD8 T cells (CCR7-CD45RO-). Litjens and colleagues attributed the change in the composition of T cell subsets in CKD patients to impaired cytokine production, especially interleukin-17 (IL-17) [25]. Similar conclusions were drawn by Yoon et al. [26].

Not only did investigators reveal the shift in CD4 and CD8 T cell composition, but they also reported that CKD and ESKD patients showed similar phenomena to the aging population: premature decline in thymic function. After reaching 40 years of age, the thymic output of new T cells (recent thymic emigrants) in the bloodstream significantly diminishes, and the maintenance of T-cell levels in circulation is sustained by homeostatic proliferation [27]. Betjes et al. investigated ESKD patients and found that they had a decreased number of recent thymic emigrants and increased homeostatic proliferation of naive T cells. They also revealed that with increased homeostatic proliferation, naive T cells in ESKD patients are more susceptible to activation-induced apoptosis [28]. It is worth noting that thymic T cell output was significantly lower in the

CKD stage 5 population compared with the healthy, age-related population, with shorter T cell telomeres in both CD4+ and CD8+ T cells [Fig. 1] [29]. Meijers et al. also confirmed the reduction of CD28 expression in CD4 and CD8 subpopulations, which implies that both CD4 and CD8 groups of cells tend to be more differentiated in patients with poor kidney function [29]. Kidney replacement therapy modalities do not affect the immunosenescence phenomenon in the CKD population. In a comparison of immunological changes between ESKD patients undergoing hemodialysis and peritoneal dialysis, no significant variations in T cell counts and aging indicators were observed, indicating that immunosenescence is a universal occurrence in ESKD patients, irrespective of the treatment approach [29,30].

Although several studies have demonstrated an association between the upregulation of T follicular helper cells (T$_{FH}$ cells) and chronic inflammation in cardiovascular and autoimmune diseases, Hartzell and colleagues reported no difference in total T$_{FH}$ (CXCR5+PD1+CD4+CD8−) levels among patients with ESKD, CKD and the healthy population. However, ESKD patients had significantly lower frequencies of T$_{FH1}$ (CCR6−CXCR3+CXCR5+PD1+CD4+CD8−) cells but more T$_{FH2}$ (CCR6−CXCR3−CXCR5+PD1+CD4+CD8−) and T$_{FH17}$ (CCR6+CXCR3−CXCR5+PD1+CD4+CD8−) cells. A previous study suggested that T$_{FH2}$ contributes to B cell maturation by aggravated B cells converting into plasma blasts in germinal centers [31], which may explain the significant increase in circulating plasmablasts observed in ESRD patients in the same study [32].

It is worth noting that uremic status also decreases TLR expression, and one of TLR's function is involved in the maturation of dendritic cells [3,33,34]. Dendritic cells, as one of the antigen-presenting cells (APC), primarily function to present antigens to lymphocytes and induce their activation. By lowering TLR expression, lymphocyte activation is reduced in infection-prone CKD and ESKD patients, which increases their susceptibility to bacterial infections.

Uremic status not only induces lymphocyte phenotype shifting and increased differentiation status, but also affects inflammatory cytokine patterns. In 2020, Hartzell and colleagues analyzed the inflammatory cytokine patterns of ESRD, CKD patients, and the healthy population, revealing that ESKD patients had significantly higher serum levels of interferon-gamma (IFN-γ), TNF-α, soluble CD40L (sCD40L), Granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin-4 (IL-4), interleukin-8 (IL-8), Monocyte chemoattractant protein-1 (MCP-1), and Macrophage inflammatory protein-1β (MIP-1β) than CKD and the healthy population. Following mitogen stimulation, CD4+ and CD8+ T cells in the ESRD group exhibited a pro-inflammatory phenotype with heightened levels of IFN-γ and TNF-α. On the other hand, both CKD and ESKD patients had elevated interleukin-2 (IL-2) levels [32]. Al-rawi et al. further reported a significant increase in IL-2 and IL-17 levels, which were paralleled with an increase in serum creatinine, urea, and urinary albumin concentration in 2022 [35].

Uremia-associated dysregulation of APCs, T cells, and cytokine expression can lead to impaired vaccine responses [36,37], increased proinflammatory status [38], and a higher risk for infection [33] and cardiovascular events [39,40]. Decreased B cell activation and increased apoptosis can also diminish serologic responses against pathogens and immunogenicity after vaccination [3]. In summary, CKD and ESKD are associated with adaptive immunosenescence, which is manifested as a decreased capacity of T and B cells against new infections, decreased naive lymphocytes, increased differentiated lymphocyte strain, and increased inflammatory cytokines.
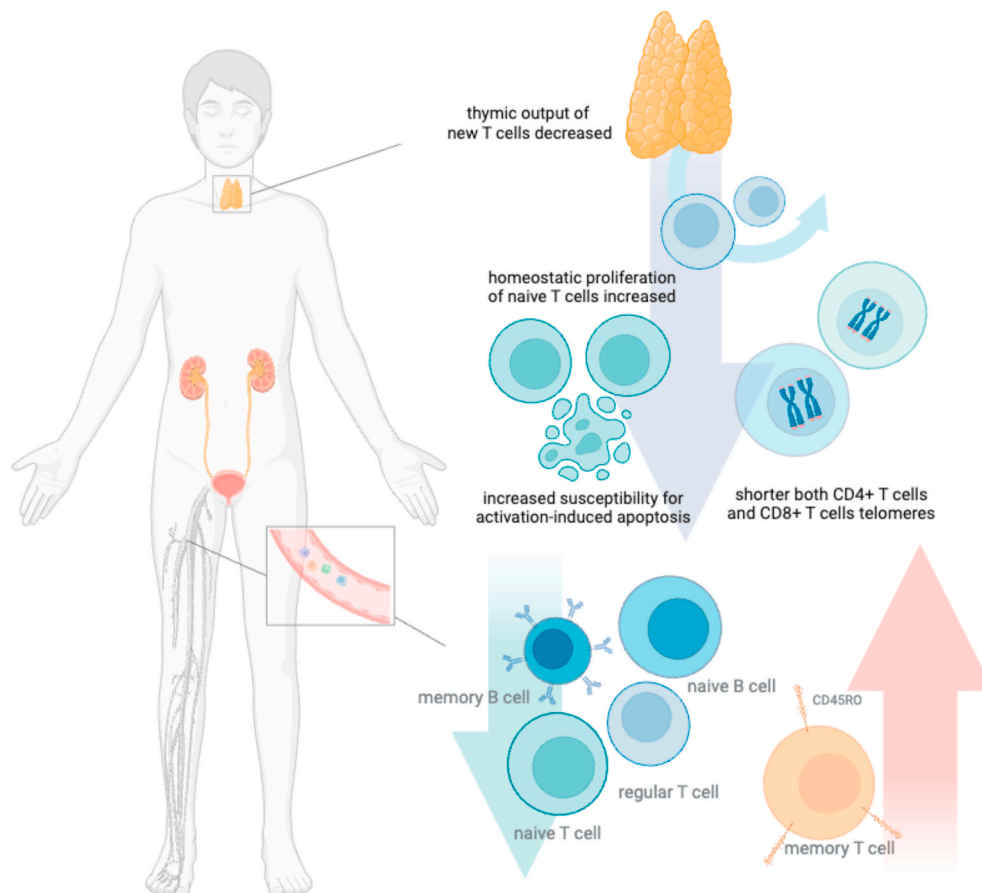

Fig. 1. The shift of lymphocytes towards a senescent and exhausted phenotype, as well as a premature decline in thymic function, in patients with chronic kidney disease (CKD).

Chronic kidney disease induces gut dysbiosis

The gut is the largest immune organ in the body, with a complex mucosal immune system. Intestinal epithelial cells directly participate in immunological surveillance and direction of host responses in the gut, and lymphocytes and innate immune cells are found throughout the epithelial layers [41]. Recent studies have revealed that not only does the complex immune system of the gut play an important role in human physiology and pathophysiology, but the trillions of microorganisms harbored by the gut also host a special role in physiological and immunological protection. Nowadays, gut microbiota is considered the bridge between aging, immune system, and kidneys. It plays a role in organ cross-talk via the gut–kidney axis and the gut–brain axis through immune regulation [42]. Gut microbiota could activate the bone marrow-derived immune cells, which could result in low-grade inflammation [42]. Yang et al. demonstrated the significant role of gut microbiota in bone formation and health, highlighting their ability to induce insulin-like growth factor-1 (IGF-1), which promotes bone formation [43]. They observed higher expression of IGF-1 in the bone marrow of mice colonized with microbiota compared to germ-free mice. Additionally, short-term colonization of microbiota led to increased expression of nuclear factor-kappaB ligand (RANKL), TNF-α, and interleukin-1 beta (IL-1β) in the colon, as well as increased RANKL expression in the bone marrow [43]. Another study by Josefsdottir et al. reported that depletion of the intestinal microbiome through broad-spectrum antibiotics resulted in the depletion of hematopoietic stem cells and impaired granulocyte maturation, which could be partially reversed by colon fecal microbiota transplantation [44]. Thus, both studies by Yang and Josefsdottir suggest that the gut microbiome plays a crucial role in bone formation, bone health, and the activity of bone marrow hematopoietic stem cells through hormone and cytokine production. In the CKD and ESKD population, several factors contribute to gut dysbiosis and increased intestinal permeability. These factors include metabolic acidosis, uremic toxins, congestion of the intestinal wall, vascular calcification associated with bowel ischemia, and frequent exposure to antibiotics [45]. The CKD diet also contributes to alterations in gut microbiota [45,46]. Animal models, as demonstrated by Andersen et al. have shown that uremia is associated with intestinal barrier disruption and translocation of intestinal bacteria, leading to increased systemic inflammation [47], which is consistent with the findings reported by Konrad [48] and Yang [49]. For short, uremia in CKD disrupts the composition of the colon microbiota and epithelial junction, leading to bacteria translocation, endotoxemia, and systemic inflammation. The translocation of bacteria has been demonstrated in early uremic animal models through direct culture methods [50], as well as through the detection of bacterial DNA from feces and circulation in animal model and patient with kidney function declined or on dialysis [51–53]. These phenomena have been proposed as leaky gut syndrome in CKD [45,54]. Although not in patients with declined kidney function, a recently published study by Bernard-Raichon provided some evidence linked between gut dysbiosis and bacteremia. By analyzing the blood culture result, they investigated paired microbiome data between gut microbiome dysbiosis and microbial bloodstream infections indicating that bacteria may translocate from the gut into the systemic circulation in coronavirus disease 2019 (COVID-19) patients [55].

Similar alterations in the adaptive immune system are observed in both the aging population and individuals with kidney failure. Additionally, these two populations also exhibit comparable changes in their gut environment. Age-related gut microbiota changes, including decreasing diversity and expansion in proteolytic bacteria, were reported in a previous study [56]. Furthermore, old age also resulted in increased gut permeability. By investigating the biomarker of plasma intestinal permeability, zonulin, previous studies have demonstrated the disruption of the gut-blood barrier in aging individuals. These studies have reported that leaky gut syndrome may play a role in the age-related increase in inflammation and frailty [57–59]. With declining kidney function, the intestinal environment was modulated. Uremia influences metabolic derangements and promotes pathogen overgrowth. In 2012, Wang and colleagues reported that all the observed genera, including *Klebsiella* spp, *Proteus* spp, *Escherichia* spp, *Enterobacter* spp, and *Pseudomonas* spp, were overgrown in the guts of ESKD patients, and bacterial DNAs can be detected in the blood of 20% of ESKD patients [51]. Besides the overgrowth of microbiota, the change in diversity and enterotype shift was also observed in CKD and ESKD patients. Jiang et al. reported that the enterotypes change from *Prevotella* to *Bacteroides* in ESRD patients compared to the healthy individual [60]. Vaziri and colleagues analyzed the stools from ESKD patients and revealed that kidney failure status significantly modifies the composition of the gut microbiome. There is a decrease in the *Lactobacillus* family and an increase in the *Enterobacteriaceae* family under uremic status [61]. Hu et al. also revealed that patients with CKD exhibited a distinct gut microbial community compared to the healthy population. CKD patients displayed lower abundances of *Candida*, *Bjerkandera*, *Rhodotorula*, and *Ganoderma*, while exhibiting a higher abundance of *Saccharomyces* [62]. Asgharian and colleagues elucidated that alterations in the gut microbiome may contribute to uremic toxicity and inflammation in individuals with ESKD. They discovered a significant positive correlation between the *Prevotellaceae* family and total antioxidant capacity, *Lactobacilli* species and C-reactive protein as well as p-cresol, and *Scardovia wiggsiae* and indoxyl sulfate (IS) [63]. In the review authored by Huang et al. it was summarized that in CKD patients, there is a noteworthy decrease in the levels of *Lactobacillus*, *Bifidobacterium*, *Bacteroides*, *Akkermansia*, *Ruminococcaceae*, and *Prevotella*, along with an elevation in *Escherichia coli* and *Enterococcus*. These findings indicate a reduction in probiotic microorganisms and an increase in the abundance of pathogenic bacteria in patients with kidney failure [64]. These studies have shown that gut dysbiosis could be one of the contributors to increased systemic inflammation in CKD or ESRD patients. D-lactate, high-sensitive C-reactive protein, and interleukin-6 levels were substantially higher in these patients, indicating the onset of systemic inflammation [51,60, 62]. Based on their research, Andersen et al. deduced that uremia is linked to intestinal dysbiosis, intestinal barrier dysfunction, and bacterial translocation, culminating in persistent systemic inflammation in CKD [47].

Not only can uremic status lead to gut dysbiosis, but gut dysbiosis can also affect kidney function. Two pathways through which gut dysbiosis can affect kidney function are metabolite and immune mediation [42, 65]. Gut dysbiosis is linked to elevated production of intestinally derived metabolites, such as p-cresol, indole, and trimethylamine (TMA), which serve as precursors of uremic toxins [66,67]. In 2015, Xu and colleagues reported that the median plasma trimethylamine-N-oxide (TMAO) level was 30.33 μmol/L in CKD patients, nearly 15-fold higher compared to healthy controls [68]. Recent studies have revealed that alterations in TMAO levels are not only associated with uremia but also with dietary modifications in human trials [69,70], as well as changes in gut microbiota composition induced by metformin [71]. Uremia can lead to gut dysbiosis, characterized by an imbalance in gut bacteria, including an expansion of certain bacteria that possess uricase, p-cresyl-forming enzymes, and indole-forming enzymes [61,72]. Intestinal bacteria play a role in the generation of gut-derived uremic toxins, such as p-cresol sulfate (PCS) and indoxyl sulfate [73]. It is hypothesized that these gut-derived uremic toxins or their precursors may leak into the systemic circulation, contributing to kidney damage and increased cardiovascular risk [74]. Furthermore, in CKD, LPS from bacteria can enter the bloodstream [65], and there may also be instances of bacterial translocation [51]. The presence of LPS or bacteria in the circulation can induce systemic inflammation, potentially leading to kidney damage. Immune-mediated kidney damage arises from the activation of immune cells in the intestine due to dysbiosis [75]. The activated immune cells increase the production of cytokines [42–44] and soluble urokinase-type plasminogen activator receptor (suPAR) [76–78], resulting in kidney inflammation. Hayek et al. also found that an increased level of suPAR

was independently linked to the development of CKD and a hastened decrease in estimated glomerular filtration rate (eGFR) [76].

Aside from CKD, it is worth noting that diet, alcohol, and various lifestyle-related factors, such as a Western diet, excessive alcohol consumption, and psychological stress, have also been associated with the development of gut dysbiosis [79]. In order to address gut dysbiosis and identify potential treatment targets for CKD, researchers have explored multiple interventions. These interventions include dietary modifications, fecal microbial transplantation, inhibitors targeting TMAO synthesis [80,81], as well as the supplementation of prebiotics or probiotics [82,83].

In brief, both age and CKD can result in gut dysbiosis and increased gut permeability, which are associated with activation of immune cells, increased production of cytokines and pro-inflammatory mediators, and local and systemic inflammation. The immune changes in aged-related gut dysbiosis and the chronic inflammation changes resulting from gut dysbiosis may also lead to CKD progression.

The clinical results of inflamm-aging in chronic kidney disease (CKD) and end stage kidney disease (ESKD) patients

The immune integrity of individuals with kidney function insufficiency is known to be compromised, and thus it is not surprising that patients with CKD and ESKD are highly susceptible to infections, exhibit reduced response to vaccination, and have an increased risk of cardiovascular events [Fig. 2] [3,4,39,84,85].

Advanced CKD is linked with an elevated risk of severe infections, such as urinary tract infections, lower respiratory tract infections, central nervous system infections, and sepsis [86]. The heightened risk of infection in advanced CKD is linked with subsequent negative outcomes. Based on their investigation of the Canadian Prospective Cohort (CanPREDDICT), Hassan and colleagues found that infectious episodes were independently associated with an elevated risk of cardiovascular ischemia, congestive heart failure, end-stage kidney disease, or

mortality [87]. As kidney function decreases, the premature alterations in the immune system, such as reduced production of new T cells from the thymus, decreased relative telomere length of T cells [29], and a more differentiated memory T-cell compartment [25,26], make patients highly vulnerable to infections. This decline in kidney function creates a vicious cycle in CKD patients.

Moreover, vaccination seems to have little effect on breaking this vicious cycle. For instance, dialysis patients have been shown to have lower protective antibody titers and an inability to maintain adequate antibody titers over time after hepatitis B virus vaccination [84,88,89]. Therefore, the Centers for Disease Control and Prevention (CDC) recommends that CKD patients receive HBV vaccination early on in the course of kidney disease and receive higher doses and/or additional boosters to achieve adequate protection [88]. While annual influenza vaccination has been recommended for dialysis patients, Remschmidt et al.'s meta-analysis indicates that the protective benefits of influenza vaccination in individuals with ESKD are restricted and of poor quality [85].

During the COVID-19 pandemic, CKD has been identified as a key risk factor for mortality [90–92]. Gansevoort and colleagues reported a graded association between the level of kidney dysfunction and the risk of COVID-19 mortality [91]. Based on the OpenSAFELY project, which examined 17 million patients, dialysis, organ transplant, and stage 4 and 5 CKD were three of the four comorbidities associated with the highest mortality risk from COVID-19 [90]. The higher risk of virus infection might be associated with the relative lowering level of T_{FH1} in CKD patients [32], which plays a pivotal role in response to viral infection [93,94]. Furthermore, studies have demonstrated that the immunogenicity rate after vaccination is lower in CKD and ESKD patients [36,95, 96]. Besides, a state of chronic systemic inflammation also increases morbidity and mortality in kidney insufficiency patients [97,98]. In brief, the phenomenon of inflamm-aging in individuals with kidney insufficiency renders this population susceptible to diminished immunogenicity following vaccination, while the presence of chronic
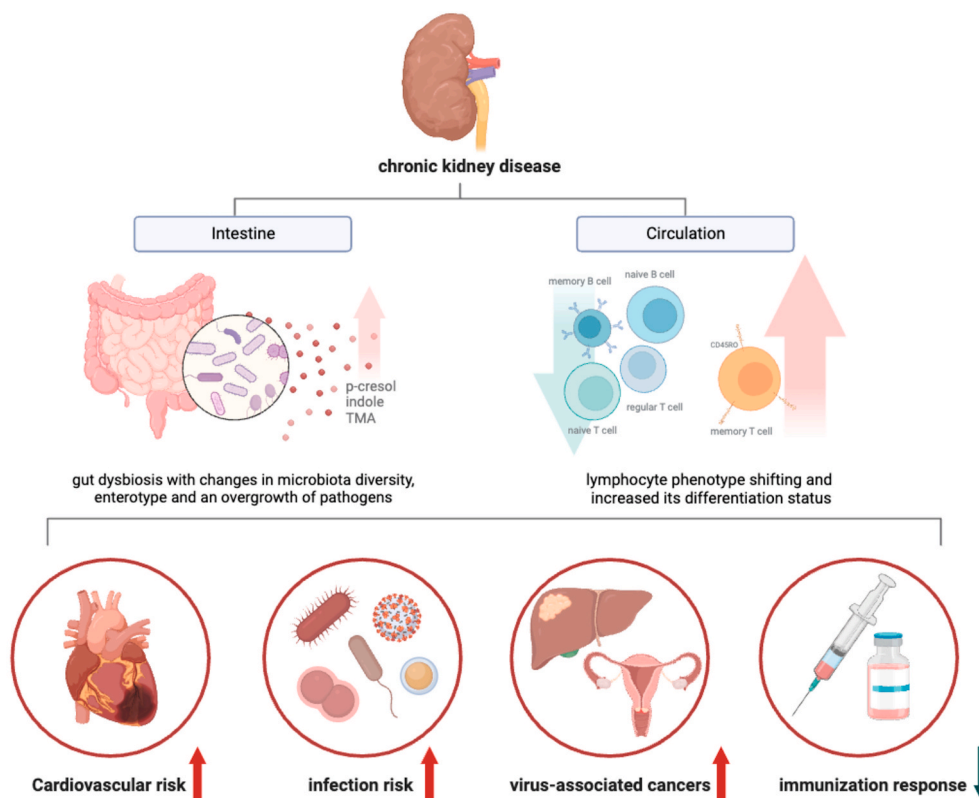

Fig. 2. The clinical outcomes of inflamm-aging in patients with chronic kidney disease (CKD) and end stage kidney disease (ESKD).

inflammation and inflamm-aging renders CKD patients prone to heightened morbidity and mortality throughout the COVID-19 pandemic.

Conclusion

CKD and ESKD patients face an immunosenescence status nearly 20 years earlier compared to age-matched healthy individuals [1]. The accumulation of uremic toxins influence the innate immunity via upregulation of chemokine/chemokine and ROS production [24], impaired phagocytosis, and impaired stimulation of T cells [20]. In adaptive immune system, uremic status shifts lymphocytes towards senescent and exhausted phenotypes, lowers thymic T cell output, and decreases the relative telomere length of T cells [28], weakening the adaptive immune system in kidney insufficiency. In addition, Uremia is also associated with gut dysbiosis, which results in alterations in the diversity and abundance of gut microbiota. These changes further enhance the production of precursors of uremic toxins, ultimately exacerbating both local and systemic inflammation. Consequently, the accumulation of gut-derived uremic toxins contributes to an accelerated decline in kidney function [64–67,76]. The immunosenescence, which results in impaired vaccine responses, increased susceptibility to infection, autoimmunity, and cancer, as well as increased cardiovascular risk, may explain the fragility and premature mortality in CKD and ESKD patients [3,4,39,84,85].

Conflicts of interest

The authors declare no conflicts of interest.

References

[1] Huang W, Hickson LJ, Eirin A, Kirkland JL, Lerman LO. Cellular senescence: the good, the bad and the unknown. Nat Rev Nephrol 2022;18(10):611–27.
[2] Levey AS, Eckardt KU, Tsukamoto Y, Levin A, Coresh J, Rossert J, et al. Definition and classification of chronic kidney disease: a position statement from Kidney Disease: improving Global Outcomes (KDIGO). Kidney Int 2005;67(6):2089–100.
[3] Syed-Ahmed M, Narayanan M. Immune dysfunction and risk of infection in chronic kidney disease. Adv Chron Kidney Dis 2019;26(1):8–15..
[4] Collins AJ, Kasiske B, Herzog C, Chavers B, Foley R, Gilbertson D, et al. Excerpts from the United States Renal Data System 2004 annual data report: atlas of end-stage renal disease in the United States. Am J Kidney Dis 2005;45(Suppl 1):S1–280.
[5] Sarnak MJ, Jaber BL. Mortality caused by sepsis in patients with end-stage renal disease compared with the general population. Kidney Int 2000;58(4):1758–64.
[6] Maisonneuve P, Agodoa L, Gellert R, Stewart JH, Buccianti G, Lowenfels AB, et al. Cancer in patients on dialysis for end-stage renal disease: an international collaborative study. Lancet 1999;354(9173):93–9.
[7] Sampani E, Stangou M, Daikidou DV, Nikolaidou V, Asouchidou D, Dimitriadis C, et al. Influence of end stage renal disease on CD28 expression and T-cell immunity. Nephrology (Carlton) 2021;26(2):185–96.
[8] Sampani E, Daikidou DV, Lioulios G, Xochelli A, Mitsoglou Z, Nikolaidou V, et al. CD28null and regulatory T cells are substantially disrupted in patients with end-stage renal disease due to diabetes mellitus. Int J Mol Sci 2021;22(6).
[9] Laude-Sharp M, Caroff M, Simard L, Pusineri C, Kazatchkine MD, Haeffner-Cavaillon N. Induction of IL-1 during hemodialysis: transmembrane passage of intact endotoxins (LPS). Kidney Int 1990;38(6):1089–94.
[10] Carracedo J, Ramirez R, Madueno JA, Soriano S, Rodriguez-Benot A, Rodriguez M, et al. Cell apoptosis and hemodialysis-induced inflammation. Kidney Int Suppl 2002;(80):89–93.
[11] Nilsson B, Ekdahl KN, Mollnes TE, Lambris JD. The role of complement in biomaterial-induced inflammation. Mol Immunol 2007;44(1–3):82–94.
[12] Morena M, Delbosc S, Dupuy AM, Canaud B, Cristol JP. Overproduction of reactive oxygen species in end-stage renal disease patients: a potential component of hemodialysis-associated inflammation. Hemodial Int 2005;9(1):37–46.
[13] Zewinger S, Schumann T, Fliser D, Speer T. Innate immunity in CKD-associated vascular diseases. Nephrol Dial Transplant 2016;31(11):1813–21.
[14] Sepe V, Libetta C, Gregorini M, Rampino T. The innate immune system in human kidney inflammaging. J Nephrol 2022;35(2):381–95.
[15] Elloumi N, Fakhfakh R, Ayadi L, Sellami K, Abida O, Ben Jmaa M, et al. The increased expression of toll-like receptor 4 in renal and skin lesions in lupus erythematosus. J Histochem Cytochem 2017;65(7):389–98.
[16] O'Sullivan KM, Ford SL, Longano A, Kitching AR, Holdsworth SR. Intrarenal Toll-like receptor 4 and Toll-like receptor 2 expression correlates with injury in antineutrophil cytoplasmic antibody-associated vasculitis. Am J Physiol Renal Physiol 2018;315(5):F1283–94.
[17] Cunningham PN, Wang Y, Guo R, He G, Quigg RJ. Role of Toll-like receptor 4 in endotoxin-induced acute renal failure. J Immunol 2004;172(4):2629–35.
[18] Gollapudi P, Yoon JW, Gollapudi S, Pahl MV, Vaziri ND. Leukocyte toll-like receptor expression in end-stage kidney disease. Am J Nephrol 2010;31(3):247–54.
[19] Xi Y, Shao F, Bai XY, Cai G, Lv Y, Chen X. Changes in the expression of the Toll-like receptor system in the aging rat kidneys. PLoS One 2014;9(5):e96351.
[20] Vaziri ND, Pahl MV, Crum A, Norris K. Effect of uremia on structure and function of immune system. J Ren Nutr 2012;22(1):149–56.
[21] Alexiewicz JM, Smogorzewski M, Fadda GZ, Massry SG. Impaired phagocytosis in dialysis patients: studies on mechanisms. Am J Nephrol 1991;11(2):102–11.
[22] Agrawal S, Gollapudi P, Elahimehr R, Pahl MV, Vaziri ND. Effects of end-stage renal disease and haemodialysis on dendritic cell subsets and basal and LPS-stimulated cytokine production. Nephrol Dial Transplant 2010;25(3):737–46.
[23] Verkade MA, van Druningen CJ, Vaessen LM, Hesselink DA, Weimar W, Betjes MG. Functional impairment of monocyte-derived dendritic cells in patients with severe chronic kidney disease. Nephrol Dial Transplant 2007;22(1):128–38.
[24] Vaziri ND. Oxidative stress in uremia: nature, mechanisms, and potential consequences. Semin Nephrol 2004;24(5):469–73.
[25] Litjens NH, van Druningen CJ, Betjes MG. Progressive loss of renal function is associated with activation and depletion of naive T lymphocytes. Clin Immunol 2006;118(1):83–91.
[26] Yoon JW, Gollapudi S, Pahl MV, Vaziri ND. Naive and central memory T-cell lymphopenia in end-stage renal disease. Kidney Int 2006;70(2):371–6.
[27] Naylor K, Li G, Vallejo AN, Lee WW, Koetz K, Bryl E, et al. The influence of age on T cell generation and TCR diversity. J Immunol 2005;174(11):7446–52.
[28] Betjes MG, Langerak AW, van der Spek A, de Wit EA, Litjens NH. Premature aging of circulating T cells in patients with end-stage renal disease. Kidney Int 2011;80 (2):208–17.
[29] Meijers RW, Litjens NH, de Wit EA, Langerak AW, van der Spek A, Baan CC, et al. Uremia causes premature ageing of the T cell compartment in end-stage renal disease patients. Immun Ageing 2012;9(1):19.
[30] Moser B, Roth G, Brunner M, Lilaj T, Deicher R, Wolner E, et al. Aberrant T cell activation and heightened apoptotic turnover in end-stage renal failure patients: a comparative evaluation between non-dialysis, haemodialysis, and peritoneal dialysis. Biochem Biophys Res Commun 2003;308(3):581–5.
[31] Morita R, Schmitt N, Bentebibel SE, Ranganathan R, Bourdery L, Zurawski G, et al. Human blood CXCR5(+)CD4(+) T cells are counterparts of T follicular cells and contain specific subsets that differentially support antibody secretion. Immunity 2011;34(1):108–21.
[32] Hartzell S, Bin S, Cantarelli C, Haverly M, Manrique J, Angeletti A, et al. Kidney failure associates with T cell exhaustion and imbalanced follicular helper T cells. Front Immunol 2020;11:583702.
[33] Ando M, Shibuya A, Tsuchiya K, Akiba T, Nitta K. Reduced expression of Toll-like receptor 4 contributes to impaired cytokine response of monocytes in uremic patients. Kidney Int 2006;70(2):358–62.
[34] Kuroki Y, Tsuchida K, Go I, Aoyama M, Naganuma T, Takemoto Y, et al. A study of innate immunity in patients with end-stage renal disease: special reference to toll-like receptor-2 and -4 expression in peripheral blood monocytes of hemodialysis patients. Int J Mol Med 2007;19(5):783–90.
[35] Al-Rawi KF, Ali HH, Guma MA, Mohammed Aldahham BJ, Tuleab Alaaraji SF, Al-Ani O, et al. Relationship between IL-2, IL-17 concentrations, and serum creatinine levels in men with chronic kidney diseases. Rep Biochem Mol Biol 2022;10(4):664–74.
[36] Chen JJ, Lee TH, Tian YC, Lee CC, Fan PC, Chang CH. Immunogenicity rates after SARS-CoV-2 vaccination in people with end-stage kidney disease: a systematic review and meta-analysis. JAMA Netw Open 2021;4(10):e2131749.
[37] Udomkarnjananun S, Takkavatakarn K, Praditpornsilpa K, Nader C, Eiam-Ong S, Jaber BL, et al. Hepatitis B virus vaccine immune response and mortality in dialysis patients: a meta-analysis. J Nephrol 2020;33(2):343–54.
[38] Witko-Sarsat V, Friedlander M, Nguyen Khoa T, Capeillere-Blandin C, Nguyen AT, Canteloup S, et al. Advanced oxidation protein products as novel mediators of inflammation and monocyte activation in chronic renal failure. J Immunol 1998;161(5):2524–32.
[39] Arici M, Walls J. End-stage renal disease, atherosclerosis, and cardiovascular mortality: is C-reactive protein the missing link? Kidney Int 2001;59(2):407–14.
[40] Girndt M, Kaul H, Sester U, Ulrich C, Sester M, Georg T, et al. Anti-inflammatory interleukin-10 genotype protects dialysis patients from cardiovascular events. Kidney Int 2002;62(3):949–55.
[41] McDermott AJ, Huffnagle G. The microbiome and regulation of mucosal immunity. Immunology 2014;142(1):24–31.
[42] Yang T, Richards EM, Pepine CJ, Raizada MK. The gut microbiota and the brain-gut-kidney axis in hypertension and chronic kidney disease. Nat Rev Nephrol 2018;14(7):442–56.

[43] Yan J, Herzog JW, Tsang K, Brennan CA, Bower MA, Garrett WS, et al. Gut microbiota induce IGF-1 and promote bone formation and growth. Proc Natl Acad Sci U S A 2016;113(47):E7554–63.

[44] Josefsdottir KS, Baldridge MT, Kadmon CS, King KY. Antibiotics impair murine hematopoiesis by depleting the intestinal microbiota. Blood 2017;129(6):729–39.

[45] Anders HJ, Andersen K, Stecher B. The intestinal microbiota, a leaky gut, and abnormal immunity in kidney disease. Kidney Int 2013;83(6):1010–6.

[46] Wang Z, Klipfell E, Bennett BJ, Koeth R, Levison BS, Dugar B, et al. Gut flora metabolism of phosphatidylcholine promotes cardiovascular disease. Nature 2011; 472(7341):57–63.

[47] Andersen K, Kesper MS, Marschner JA, Konrad L, Ryu M, Kumar Vr S, et al. Intestinal dysbiosis, barrier dysfunction, and bacterial translocation account for CKD-related systemic inflammation. J Am Soc Nephrol 2017;28(1):76–83.

[48] Konrad L, Andersen K, Kesper MS, Kumar SV, Mulay SR, Anders HJ. The gut flora modulates intestinal barrier integrity but not progression of chronic kidney disease in hyperoxaluria-related nephrocalcinosis. Nephrol Dial Transplant 2020;35(1): 86–97.

[49] Yang J, Lim SY, Ko YS, Lee HY, Oh SW, Kim MG, et al. Intestinal barrier disruption and dysregulated mucosal immunity contribute to kidney fibrosis in chronic kidney disease. Nephrol Dial Transplant 2019;34(3):419–28.

[50] de Almeida Duarte JB, de Aguilar-Nascimento JE, Nascimento M, Nochi Jr RJ. Bacterial translocation in experimental uremia. Urol Res 2004;32(4):266–2770.

[51] Wang F, Jiang H, Shi K, Ren Y, Zhang P, Cheng S. Gut bacterial translocation is associated with microinflammation in end-stage renal disease patients. Nephrology (Carlton) 2012;17(8):733–8.

[52] Wang F, Zhang P, Jiang H, Cheng S. Gut bacterial translocation contributes to microinflammation in experimental uremia. Dig Dis Sci 2012;57(11):2856–62.

[53] Shi K, Wang F, Jiang H, Liu H, Wei M, Wang Z, et al. Gut bacterial translocation may aggravate microinflammation in hemodialysis patients. Dig Dis Sci 2014;59 (9):2109–17.

[54] Vaziri ND, Zhao YY, Pahl MV. Altered intestinal microbial flora and impaired epithelial barrier structure and function in CKD: the nature, mechanisms, consequences and potential treatment. Nephrol Dial Transplant 2016;31(5): 737–46.

[55] Bernard-Raichon L, Venzon M, Klein J, Axelrad JE, Zhang C, Sullivan AP, et al. Gut microbiome dysbiosis in antibiotic-treated COVID-19 patients is associated with microbial translocation and bacteremia. Nat Commun 2022;13(1):5926.

[56] Claesson MJ, Cusack S, O'Sullivan O, Greene-Diniz R, de Weerd H, Flannery E, et al. Composition, variability, and temporal stability of the intestinal microbiota of the elderly. Proc Natl Acad Sci U S A 2011;108(Suppl 1):4586–91.

[57] Qi Y, Goel R, Kim S, Richards EM, Carter CS, Pepine CJ, et al. Intestinal permeability biomarker zonulin is elevated in healthy aging. J Am Med Dir Assoc 2017;18(9):810. e1–4.

[58] Sturgeon C, Fasano A. Zonulin, a regulator of epithelial and endothelial barrier functions, and its involvement in chronic inflammatory diseases. Tissue Barriers 2016;4(4):e1251384.

[59] Fasano A. Zonulin and its regulation of intestinal barrier function: the biological door to inflammation, autoimmunity, and cancer. Physiol Rev 2011;91(1):151–75.

[60] Jiang S, Xie S, Lv D, Wang P, He H, Zhang T, et al. Alteration of the gut microbiota in Chinese population with chronic kidney disease. Sci Rep 2017;7(1):2870.

[61] Vaziri ND, Wong J, Pahl M, Piceno YM, Yuan J, DeSantis TZ, et al. Chronic kidney disease alters intestinal microbial flora. Kidney Int 2013;83(2):308–15.

[62] Hu J, Wei S, Gu Y, Wang Y, Feng Y, Sheng J, et al. Gut mycobiome in patients with chronic kidney disease was altered and associated with immunological profiles. Front Immunol 2022;13:843695.

[63] Asgharian M, Gholizadeh P, Samadi Kafil H, Ghojazadeh M, Samadi A, Soleymani J, et al. Correlation of inflammatory biomarkers with the diversity of Bacteroidaceae, Bifidobacteriaceae, Prevotellaceae and Lactobacillaceae families in the intestinal microbiota of patients with end stage renal disease. Adv Med Sci 2022;67(2):304–10.

[64] Huang Y, Xin W, Xiong J, Yao M, Zhang B, Zhao J. The intestinal microbiota and metabolites in the gut-kidney-heart Axis of chronic kidney disease. Front Pharmacol 2022;13:837500.

[65] Evenepoel P, Poesen R, Meijers B. The gut-kidney axis. Pediatr Nephrol 2017;32 (11):2005–14.

[66] Kikuchi M, Ueno M, Itoh Y, Suda W, Hattori M. Uremic toxin-producing gut microbiota in rats with chronic kidney disease. Nephron 2017;135(1):51–60.

[67] Xu KY, Xia GH, Lu JQ, Chen MX, Zhen X, Wang S, et al. Impaired renal function and dysbiosis of gut microbiota contribute to increased trimethylamine-N-oxide in chronic kidney disease patients. Sci Rep 2017;7(1):1445.

[68] Tang WH, Wang Z, Kennedy DJ, Wu Y, Buffa JA, Agatisa-Boyle B, et al. Gut microbiota-dependent trimethylamine N-oxide (TMAO) pathway contributes to both development of renal insufficiency and mortality risk in chronic kidney disease. Circ Res 2015;116(3):448–55.

[69] Argyridou S, Davies MJ, Biddle GJH, Bernieh D, Suzuki T, Dawkins NP, et al. Evaluation of an 8-week vegan diet on plasma trimethylamine-N-oxide and postchallenge glucose in adults with dysglycemia or obesity. J Nutr 2021;151(7): 1844–53.

[70] Crimarco A, Springfield S, Petlura C, Streaty T, Cunanan K, Lee J, et al. A randomized crossover trial on the effect of plant-based compared with animal-based meat on trimethylamine-N-oxide and cardiovascular disease risk factors in generally healthy adults: study with Appetizing Plantfood-Meat Eating Alternative Trial (SWAP-MEAT). Am J Clin Nutr 2020;112(5):1188–99.

[71] Su C, Li X, Yang Y, Du Y, Zhang X, Wang L, et al. Metformin alleviates choline diet-induced TMAO elevation in C57BL/6J mice by influencing gut-microbiota composition and functionality. Nutr Diabetes 2021;11(1):27.

[72] Wong J, Piceno YM, DeSantis TZ, Pahl M, Andersen GL, Vaziri ND. Expansion of urease- and uricase-containing, indole- and p-cresol-forming and contraction of short-chain fatty acid-producing intestinal microbiota in ESRD. Am J Nephrol 2014;39(3):230–7.

[73] Patel KP, Luo FJ, Plummer NS, Hostetter TH, Meyer TW. The production of p-cresol sulfate and indoxyl sulfate in vegetarians versus omnivores. Clin J Am Soc Nephrol 2012;7(6):982–8.

[74] Lau WL, Chang Y, Vaziri ND. The consequences of altered microbiota in immune-related chronic kidney disease. Nephrol Dial Transplant 2021;36(10):1791–8.

[75] Chi M, Ma K, Wang J, Ding Z, Li Y, Zhu S, et al. The immunomodulatory effect of the gut microbiota in kidney disease. J Immunol Res 2021;2021:5516035.

[76] Hayek SS, Sever S, Ko YA, Trachtman H, Awad M, Wadhwani S, et al. Soluble urokinase receptor and chronic kidney disease. N Engl J Med 2015;373(20): 1916–25.

[77] Hahm E, Wei C, Fernandez I, Li J, Tardi NJ, Tracy M, et al. Bone marrow-derived immature myeloid cells are a main source of circulating suPAR contributing to proteinuric kidney disease. Nat Med 2017;23(1):100–6.

[78] Hayek SS, Quyyumi AA, Reiser J. Soluble urokinase receptor and chronic kidney disease. N Engl J Med 2016;374(9):891.

[79] Martel J, Chang SH, Ko YF, Hwang TL, Young JD, Ojcius DM. Gut barrier disruption and chronic disease. Trends Endocrinol Metab 2022;33(4):247–65.

[80] Gupta N, Buffa JA, Roberts AB, Sangwan N, Skye SM, Li L, et al. Targeted inhibition of gut microbial trimethylamine N-oxide production reduces renal tubulointerstitial fibrosis and functional impairment in a murine model of chronic kidney disease. Arterioscler Thromb Vasc Biol 2020;40(5):1239–55.

[81] Vijay A, Valdes AM. Role of the gut microbiome in chronic diseases: a narrative review. Eur J Clin Nutr 2022;76(4):489–501.

[82] Ebrahim Z, Proost S, Tito RY, Raes J, Glorieux G, Moosa MR, et al. The effect of ß-glucan prebiotic on kidney function, uremic toxins and gut microbiome in stage 3 to 5 chronic kidney disease (CKD) predialysis participants: a randomized controlled trial. Nutrients 2022;14(4):805.

[83] Liu S, Liu H, Chen L, Liang SS, Shi K, Meng W, et al. Effect of probiotics on the intestinal microbiota of hemodialysis patients: a randomized trial. Eur J Nutr 2020; 59(8):3755–66.

[84] Courouce AM, Jungers P, Benhamou E, Laplanche A, Crosnier J. Hepatitis B vaccine in dialysis patients. N Engl J Med 1984;311(23):1515–6.

[85] Remschmidt C, Wichmann O, Harder T. Vaccines for the prevention of seasonal influenza in patients with diabetes: systematic review and meta-analysis. BMC Med 2015;13:53.

[86] McDonald HI, Thomas SL, Nitsch D. Chronic kidney disease as a risk factor for acute community-acquired infections in high-income countries: a systematic review. BMJ Open 2014;4(4):e004100.

[87] Cheikh Hassan HI, Tang M, Djurdjev O, Langsford D, Sood MM, Levin A. Infection in advanced chronic kidney disease leads to increased risk of cardiovascular events, end-stage kidney disease and mortality. Kidney Int 2016;90(4):897–904.

[88] Rangel MC, Coronado VG, Euler GL, Strikas RA. Vaccine recommendations for patients on chronic dialysis. The advisory committee on immunization practices and the American academy of pediatrics. Semin Dial 2000;13(2):101–7.

[89] Ayub MA, Bacci MR, Fonseca FL, Chehter EZ. Hemodialysis and hepatitis B vaccination: a challenge to physicians. Int J Gen Med 2014;7:109–14.

[90] Williamson EJ, Walker AJ, Bhaskaran K, Bacon S, Bates C, Morton CE, et al. Factors associated with COVID-19-related death using OpenSAFELY. Nature 2020;584 (7821):430–6.

[91] Gansevoort RT, Hilbrands LB. CKD is a key risk factor for COVID-19 mortality. Nat Rev Nephrol 2020;16(12):705–6.

[92] Pakhchanian H, Raiker R, Mukherjee A, Khan A, Singh S, Chatterjee A. Outcomes of COVID-19 in CKD patients: a multicenter electronic medical record Cohort study. Clin J Am Soc Nephrol 2021;16(5):785–6.

[93] Crotty S. T follicular helper cell differentiation, function, and roles in disease. Immunity 2014;41(4):529–42.

[94] Baiyegunhi O, Ndlovu B, Ogunshola F, Ismail N, Walker BD, Ndung'u T, et al. Frequencies of circulating Th1-biased T follicular helper cells in acute HIV-1 infection correlate with the development of HIV-specific antibody responses and lower set point viral load. J Virol 2018;92(15):e00659–18.

[95] Yang X, Zhang H, Bao W, Fu S, Jin H. Immunogenicity rates after SARS-CoV-2 three-dose vaccination in patients under dialysis: a systematic review and meta-analysis. Vaccines 2022;10(12):2070.

[96] Babel N, Hugo C, Westhoff TH. Vaccination in patients with kidney failure: lessons from COVID-19. Nat Rev Nephrol 2022;18(11):708–23.

[97] D'Marco L, Puchades MJ, Romero-Parra M, Gimenez-Civera E, Soler MJ, Ortiz A, et al. Coronavirus disease 2019 in chronic kidney disease. Clin Kidney J 2020;13 (3):297–306.

[98] Kurts C, Panzer U, Anders HJ, Rees AJ. The immune system and kidney disease: basic concepts and clinical implications. Nat Rev Immunol 2013;13(10):738–53.