

A Review of Chronic Kidney Disease and the Immune System: A Special Form of Immunosenescence

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Abstract

Immune dysregulation is a common problem and immunosenescence plays a major role in the aged population. Many chronic inflammatory diseases have the same effect in the aged such as chronic HIV-treated patients, tuberculosis patients or those with chronic kidney disease. Chronic kidney disease patients have a high incidence of vascular calcification, accelerated atherosclerosis, loss of appetite, increased muscle catabolism, renal osteodystrophy, and a high prevalence of depression because of the dysregulation of the immune system. These patients have different immune system manifestations compared with aged individuals of the same age; moreover, many geriatric syndromes are observed in this group. This review is an analysis from the nephrology perspective on the relationship between chronic kidney disease and the immune system.

Keywords: Chronic kidney disease; Aging; Immunosenescence, Geriatric syndromes

Introduction

Chronic kidney disease (CKD) and end-stage renal disease (ESRD) are increasingly common diseases in the 21st century. CKD is defined according to the level of glomerular filtration rate (GFR) and/or the presence of pathological damage or markers of kidney damage such as proteinuria or hematuria for 3 months [1]. These diseases are frequently noted in the aging population. While discussing “aging”, the chronological age of patients must be considered. Many CKD and ESRD patients become biologically senescent despite their younger chronological age. Clinical acumen indicates that ESRD patients are generally biologically older than non-ESRD individuals with similar chronological ages. ESRD patients have significant immune dysregulation compared with the general population and subsequently, have a higher susceptibility to infection and a high incidence of malignancy and cardiovascular disease, and a poor response to vaccination [2-5].

As with HIV patients receiving long-term treatment, CKD patients remain at a higher than expected risk of numerous complications typically associated with aging, including cardiovascular disease, cancer, osteoporosis, and other end-organ diseases. These changes are consistent with some of the changes to the adaptive immune system and are likely related in part to persistent microinflammation [6]. Chronic inflammation, characterized by the increased serum levels of tumor necrosis factor (TNF)- α , interleukin (IL)-6, C-reactive protein (CRP), plasminogen activator inhibitor-1, and the presence of inflammatory-related diseases, is commonly seen in aging and CKD patients. Both the dysregulation of immune cells and phenotypic changes in parenchymal cells may contribute to chronic inflammation. Moreover, senescent cells are an important source of inflammatory factors [7]. Here, we discuss CKD and ESRD patients—a different type of aging group—and immunosenescence in several body parts.

Aging and its Impact on the Kidney

Age-dependent biological changes can affect susceptibility and response of the kidney to injurious stimuli. The cellular changes in the aging kidney may diminish proliferative reserve, increase apoptosis, alter growth factor profiles, and change potential progenitor and

immune cell functions [8]. Injury and loss of podocytes are leading factors of glomerular disease and renal failure. Autophagy, a critical homeostatic and quality control mechanism maintaining glomerular homeostasis, is noted in the aging kidney, particularly in the podocyte [9,10]. Interstitial renal fibrosis is a feature of the aging kidney and is the final common pathway for the development of ESRD that is characterized by proliferation and transformation of fibroblasts into myofibroblasts, deposition of fibronectin and collagens I and III into the interstitium, and microvascular rarefaction [11]. Aging comprises a permanent low-grade activation of the inflammatory system, dysfunctionality of T cells, defective natural killer cells, and atrophy of the thymus. In the kidney, the proinflammatory M1 macrophages are deleterious during the early phase of ischemia/reperfusion injury [12] although they may eventually transition to an anti-inflammatory phenotype and subsequently exert important reparative functions [13]. Macrophages change their phenotype significantly with aging, and their functional adaptability decreases [14]. An imbalance between the production of free radicals and antioxidant defenses of aging affects the immune system. The formation of advanced glycation end products (AGEs) can alter cell functions and cause a constantly and inappropriately stimulate cells, leading to telomere shortening.

Aging is associated with multiple changes in the proliferative and functional abilities of the immune system that are not related to any pathology, but are consequences in immunosenescence and inflammation. Age-related immunosenescence in the adaptive immune system has been extensively documented, particularly with regard to T-cell apoptosis [15,16]. Many studies demonstrate that dysregulation

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Received October 27, 2013; **Accepted** January 15, 2014; **Published** January 17, 2014

Citation: Hsu HW, Lang CL, Wang MH, Chiang CK, Lu KC (2014) A Review of Chronic Kidney Disease and the Immune System: A Special Form of Immunosenescence. J Gerontol Geriat Res 3: 144. doi:10.4172/2167-7182.1000144

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of cytokines is prevalent in the biological normal elderly patients and dialysis patients. Healthy aging adults have higher levels of IL-6, IL-8, IL-10, and TNF- α ; lesser levels of IL-1 in their plasma or serum [17]; and decreased IL-2 expression in T cells [18] than prematurely aging adults. In the aged population, a switch from a T helper (Th)-1 cytokine response to a Th-2 cytokine response is found [19] and Th-17 cells are significantly increased in older individuals, whereas levels of regulatory T cells (Treg) are reduced. The changes of the Th-17/Treg ratios, in combination with altered cytokine expression during aging, may contribute to an imbalance between the pro-inflammatory and the anti-inflammatory immune response. This suggests a high susceptibility to inflammatory diseases with increasing age [20].

Immune Dysregulation in CKD Patients

Uremia and its treatment can alter the immune system in hemodialysis patients [21]. Several factors influence immunity in these patients, such as uremic toxin, malnutrition, chronic inflammation, vitamin D-parathyroid hormone axis alternation, and therapeutic dialysis [22-24]. Many studies have shown that both naive and acquired immune systems are impaired in these patients. This condition involves the coexistence of chronic immune activation (persistent hypercytokinemia and acute-phase protein response) and chronic immune suppression (poor vaccination response and a high incidence of infection and malignancy).

Monocytes and monocyte-derived dendritic cells of CKD patients have impaired endocytosis and maturation [25]. CKD patients also have lower percentages of peripheral CD4+ and CD8+ T cells and B cells in the blood [26]. Further, soluble B cell markers increase in CKD patients [27]; however, studies have also shown an increased incidence of apoptosis in B cells [28]. ESRD patients have increased apoptosis and diminished populations of naive and central memory T cells [29]. They also have impaired antigen-specific memory CD4+ T cells [30]. In dialysis patients, Th-1 lymphocytes have a decreased expression of the anti-apoptotic molecule Bcl-2, which makes the Th-1 cells more susceptible to apoptosis [31]. The decline in levels of Th-1 cells and enhancement of Th-2 differentiation has also been noted in CKD and dialysis patients [32-34]. Our previous study indicated that levels of Th-17 cells are increased and levels of Treg cells decreased in chronic hemodialysis (HD) patients (Lang CL et al., [33] 2013 in press). The functional imbalance of Th-17/Treg in uremic patients has been associated with the development of acute cardiovascular events, myocardial injury, and microinflammation [35,36]. In most CKD with type 2 diabetes patients, lots of circulating cytokines and acute phase proteins provides the immune dysfunction. The cardio-renal-metabolic risk factors, including the platelet-activating factor, acetylhydrolase, creatinine, thyroid stimulating hormone, acylation-stimulating protein, asymmetric dimethylarginine, and serum lipoprotein[Lp] (a) are triggers of systemic low-grade inflammation and enhanced autoimmune reactions [37]. In a large prospective cohort study also showed that low high-density lipoprotein cholesterol and average apolipoprotein A-I and Lp(a) concentrations implicating impaired atheroprotective properties, especially in the women with the lowest creatinine levels [38].

Pre-activated monocytes overproduce cytokines such as TNF- α , IL-1, IL-6, and IL-10 [39,40]. TNF- α and IL-1 are the major cytokines produced by activating the toll-like receptor (TLR) signaling pathway, the key receptor recognizing by the lipopolysaccharides (LPS) [41]. IL-6, a pro-inflammatory cytokine, also plays the key role in atherosclerosis and protein-energy wasting and is elevated in CKD patients [42-44].

Serum IL-12 and IL-18 levels are increased in CKD patients, and both are correlated with the inflammatory process [45,46]. Furthermore, high levels of pro-inflammatory cytokines (IL-1, IL-6, and TNF- α) and low levels of anti-inflammatory cytokines (IL-4, IL-5, and CH50) are also found in hemodialysis patients [47].

In addition to uremic toxins, dialysis-related factors such as bio-incompatibility with the hemodialysis dialyzer, endotoxins in the water, access-related infection, glucose degradation products in the peritoneal dialysis solution, and AGEs, all of which will induce chronic inflammation and activate the immune response. Together, these findings indicate that CKD patients have immune dysregulation at the cellular level and hypercytokinemia. Immunosenescence in chronic HD patients includes the loss of CD28 expression, a skewed immune repertoire to the Th-2 type, a deficient T cell-dependent immune response, and altered cytokine expression [2,16]. Nonspecific sequels of the aging process and HD such as oxidative stress and glycation may affect cells of the adaptive immune system [2,48,49]. Free radicals, AGEs, and oxidative stress are common in our chronic HD patients, and many studies have shown that their effects are attenuated in chronic HD patients [50,51]. Therefore, HD patients are also believed to be immunosenescent.

Geriatric Syndromes in CKD Patients

In CKD patients, biological aging has many presentations [52]. First, accelerated aging is the exponential increase in mortality in dialysis patients when compared with the general population at similar chronological ages. An independent review of a large community-based population found that reduced estimated GFR was associated with the risk of death, cardiovascular events, and hospitalization [53]; Second, CKD patients have an increased susceptibility to disease, similar to the geriatric population. Large surveys comparing the general and ESRD populations have demonstrated that the risk of cardiovascular, as well as infectious morbidity and mortality, is greatly increased in the ESRD population [54]; Third, many geriatric syndromes, such as frailty, cognitive dysfunction, malnutrition, cachexia/wasting, and sarcopenia are frequently seen in CKD or ESRD patients in contrast to age-matched controls [55-57].

Frailty is a biological syndrome of decreased reserve and resistance to stressors that result from cumulative declines across multiple physiological systems and causes vulnerability to adverse outcomes. Frailty is common among CKD patients on conservative treatment and dialysis, even in those who are not elderly. In a prospective cohort study, adults of all ages undergoing HD have a high prevalence of frailty, more than five times as high as community-dwelling older adults. In this population, regardless of age, frailty is a strong, independent predictor of mortality and number of hospitalizations [58]. The risk of frailty includes lower serum levels of hemoglobin and the increased prevalence of high levels of parathyroid hormone and low levels of serum vitamin D [59]. Frailty is associated with adverse outcomes among incident dialysis patients, including higher risk of hospitalization and death [60]. However, there are no data to suggest that frail patients derive any benefit from early initiation of dialysis either in the form of improved survival or functional status. They may be associated with protein-energy wasting (PEW), sarcopenia, dynapenia, and other complications of CKD. Frailty and PEW in elderly CKD patients are associated with impaired physical performance, disability, poor quality of life, and reduced survival [61]. Wasting/cachexia are prevalent among CKD patients. This is to be distinguished from malnutrition, which is defined as a consequence of insufficient food intake or an

improper diet. In malnutrition, fat mass is preferentially lost, and lean body mass and muscle mass is preserved. In cachexia/wasting, muscle is wasted and fat is relatively underutilized. Restoring adequate food intake or altering the composition of the diet reverses malnutrition but does not totally reverse cachexia/wasting. Muscle wasting in uremic patients is frequently found and has a multifactorial etiology. These factors include hormonal, immunologic and myocellular changes, metabolic acidosis, reduced protein intake, and possible physical inactivity. Wasting surrogates such as serum albumin and prealbumin show a strong association with mortality, making them robust outcome predictors [62]. Uremic sarcopenia presents a high probability of morbidity and mortality and consequently a high priority for muscle wasting prevention and treatment in these patients [63]. Conversely, malnutrition-inflammation-atherosclerosis (MIA) syndrome is also highly prevalent in CKD patients. MIA syndrome is a well-known non-traditional risk factor in cardiovascular disease (CVD), and may cause progressive atherosclerotic CVD and malnutrition [64]. Malnutrition may worsen patient outcome by aggravating existing inflammation and heart failure, accelerating atherosclerosis and increasing susceptibility to infection [65].

Depression is a common, under-recognized, and under-treated problem that is independently associated with increased morbidity and mortality in CKD patients. Patients with predialysis CKD have a high prevalence of depression and anxiety, which are associated with a reduced quality of life [66,67]. Maintenance hemodialysis in patients who have symptoms of depression may have higher levels of serum IL-6 and lower levels of serum albumin than those without symptoms [68]. In addition, epidemiologic data suggest that individuals at all stages of CKD have a higher risk of developing cognitive disorders and dementia. This risk is generally explained by the high prevalence of both symptomatic and subclinical ischemic cerebrovascular lesions [69]. CKD affects 45% persons older than 70 years of age and can double the risk for physical impairment, cognitive dysfunction, and frailty [70]. In a prospective Singapore longitudinal aging study, CKD in older persons was significantly associated with cognitive and functional decline [71]. It is related to a wide range of deficits in cognitive functioning, including verbal and visual memory and organization, and components of executive functioning and fluid intellect. In general, before treatment with hemodialysis or transplantation, the magnitude of effect with relation to CKD and function are small or modest in persons free from acute stroke and dementia [72]. A meta-analysis of cross-sectional and longitudinal studies comprising 54,779 participants, suggested an association of cognitive decline in CKD patients compared with patients without CKD (OR 1.65, 95% confidence interval (CI) 1.32-2.05; $p < 0.001$; OR 1.39, 95% CI 1.15-1.68; $p < 0.001$, respectively) [73]. In Taiwan that has the highest prevalence rate of ESRD worldwide, the incidence of dementia was higher in the CKD cohort than in the non-CKD cohort (9.30 vs. 5.55 per 1,000 person-years), with an overall hazard ratio (HR) of 1.41 (95% confidence interval (CI), 1.32-1.50), controlling for sex, age, comorbidities, and medications [74]. Therefore, CKD is a significant and independent somatic risk factor in the development of cognitive decline.

Aging and the Effects of CKD on Kidney Transplantation and Immunization

Aging affects all components of the immune response and has a major impact on transplant outcome and organ quality. Understanding how the immune system changes with increasing age will help to define

the risks of organ rejection and infection in the elderly population and will focus attention on the need for individualized immunosuppression therapy for patients in this age group [75,76]. Older patients receiving kidney transplants have a compromised T-cell effector immune response with an intact regulatory and memory T-cell response [77]. Organs from older individuals that are transplanted into young recipients have the highest rejection rates, and this effect is blunted when these organs are transplanted into old recipients. Older recipients receiving such organs have excellent rates of graft acceptance and overall survival rates [78]. Immunosenescence provides a basis for an age-adapted immunosuppression and organ allocation with the goal to optimize utilization and to improve outcomes in older recipients [76,79].

Patients with CKD and ESRD may not respond as well to vaccines as patients without kidney failure; however, adequate seroresponse rates with standard or augmented regimens for vaccinations against influenza, hepatitis B, pneumococcus, and varicella have been documented. Influenza infection remains a major public health concern worldwide. The overall body of evidence suggests that older adults are more prone to infection by the influenza virus than younger adults. Influenza prevention strategies are mainly based on immunization; however, current influenza vaccines do not offer optimal protection in this population due, in part, to waning immunity [19], and vitamin D may play an immunomodulatory role [80]. Immune response to influenza vaccination may be suboptimal in hemodialysis patients, and the administration of an additional second dose of vaccine does not improve the humoral response [81]. Other vaccines, such as hepatitis B and pneumococcal vaccines, require more frequent and/or higher doses to produce and maintain protective antibody levels [82]. CKD patients should be vaccinated in early stages of their disease, because a high GFR is more likely to be associated with the responsiveness to vaccination, particularly with the hepatitis B vaccine [83,84]. The majority of CKD patients produce a good antibody response to the pneumococcal capsular polysaccharide vaccine (PPV23); however, a substantial proportion of patients fail to mount an adequate antibody response to PPV23 and remained at significant risk of pneumococcal infection [85].

Conclusion

Uremia and the therapeutic approach utilized may influence immunity at the cellular level and clinical conditions, and CKD is another form of immunosenescence. A large amount of evidence has noted convincing similarities between CKD and aging. Accelerated aging due to CKD is an important factor as these chronologically young patients have the biological characteristics of aged patients. Many clinical problems such as arterial stiffness, atherosclerotic cardiovascular disease, and poor vaccination response are quite common in CKD patients, and many geriatric syndromes such as frailty, cognitive dysfunction, and malnutrition are frequently seen in this group. Micro-inflammation is viewed as a non-traditional cardiovascular disease risk factor in CKD patients and CKD is another type of non-traditional risk factor in aging. As nephrologists, we are continually looking for ways to improve the immune system of patients and patient outcome, and as gerontologists, we need to pay more attention to the treatment of these "biologically" aged patients and to improve their immunity in the future.

Acknowledgments

This study was sponsored by grants from Department of Medical Research of Cardinal Tien Hospital, Yonghe Branch (R102-0003).

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This article was originally published in a special issue, **Aging and Immunization** handled by Editor(s). Dr. Pierre Olivier Lang, Medical school and University hospitals of Geneva, Switzerland