Effects of Aging on Renal Function and Regenerative Capacity

Emaad M. Abdel-Rahman Mark D. Okusa

Division of Nephrology, Center for Immunity, Inflammation, and Regenerative Medicine, University of Virginia Health System, Charlottesville, Va., USA

Key Words

Aging · Kidney · Renal function · Regenerative capacity

Abstract

Along with the increase in aging of our population, the proportion of older patients with chronic kidney disease (CKD) and end-stage renal disease (ESRD) is on the rise as a result of the accumulation of comorbidities as well as biological processes associated with aging. Older patients with acute kidney injury (AKI) comprise an increasing proportion of patients with CKD/ESRD as well. In this review, we will discuss biological processes of aging that predispose patients to AKI and CKD.

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Introduction

Kidney disease has grown into an epidemic, and even more so in the older population. The number of older patients with end-stage renal disease (ESRD) is staggering, which poses a major challenge to the health care system and the community at large. We will review the epidemi-

ology of acute kidney injury (AKI), chronic kidney disease (CKD), and ESRD in older patients, the morphological and functional changes that occur in the kidney with aging, the mechanism of aging and finally the potential therapeutic agents that may play a role in modulating kidney repair in aging.

Epidemiology of Kidney Disease in the Older Population

In 1994, the US Census Bureau reported that the older population (defined here as 65 years and older) was 36.5 million [1]. Subsequent data show that the older population continues to increase, now exceeding 41.5 million, comprising about 18.3% of the total US population [2]. The burden of AKI in the general population is captured by the National Hospital Discharge Survey, National Center for Health Statistics, and indicates that the num-

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Table 1. Structural and functional changes in the aging kidney

Structural changes	Functional changes
Glomeruli	
Decreased kidney weight and volume	Decreased GFR
Glomerulosclerosis	Decreased RPF
Cortical atrophy and loss of renal parenchyma	Increased filtration fraction
Capillary tuft collapse	
Increased GBM	
GBM	
Deposition of hyaline in GBM	
Change in GBM composition	
Tubulointerstitium	
Interstitial fibrosis	Impaired water, electrolyte, and glucose handling
Tubular atrophy	Decreased diluting and concentrating capacity
Vascular	
Intrarenal arteriosclerosis	Renal vasoconstriction
Thickened intima	Decreased plasma renin activity and aldosterone
Obliteration of afferent and efferent arterioles	Increased angiotensin II and endothelin
	Decreased vasodilator activity of prostacyclin
GBM = Glomerular basement membrane; GFR = glomerular filtration rate; RPF = renal plasma flow.	

ber of hospitalized patients with a diagnosis of AKI (ICD9 = 584.0–584.9) has increased over the last 20 years, from 161,000 in 1990 to 2.7 million in 2010. This represents ~7% of hospitalized patients. Prevalence of ESRD increased from 290/million in 1980 to 1,738/million in 2008, an increase of 6,000% [3]. This growth in the older population parallels the increase in the number of older patients with kidney disease. This increase in the overall number of patients with kidney disease is a function of aging. In 2011, among Medicare patients, AKI increased from 14.9/1,000 patient years for patients aged 66–69 years to 18.8, 26.4, 35.9, and 49.6/1,000 patient years for patients aged 70–74, 75–79, 80–84, and >85 years, respectively [3]. Similarly, the prevalence of CKD increased from 5.7 for patients aged 20–39 years to 36.5 for patients >60 years, and the incidence of ESRD increased from 156/million at age 0–19 years, to 127/million at age 20–49 years, and to 571 and 1,307/million for patients aged 45–64 and 65–74 years, respectively [3]. While these data demonstrate that older individuals are more prone to have kidney disease, it is worthwhile to note that in the Baltimore Longitudinal Study, a cohort study conducted between 1958 and 1981 that followed older individuals for 8 or more years, one third of these individuals had no decrease in their renal function, which was measured by creatinine clearance, and a small segment of this population showed improvement in their renal function [4].

Structural and Functional Changes in the Kidney with Aging

While the numbers of glomeruli among individuals range between 250,000 to more than 1.5 million per kidney at birth, it decreases with age at a rate of approximately 6,752 glomeruli/year after the age of 18 years [5]. Renal mass also shows a decrease from >400 g during the 3rd and 4th decade to <300 g by the 9th decade [6]. These morphological changes are usually accompanied by several histological changes in the glomeruli, glomerular basement membrane, tubulointerstitium as well as the renal vasculature. These morphological and histological changes are mirrored by functional changes in these structures [7–9]. Table 1 summarizes some of these structural and functional changes noted in the aging kidney.

Mechanism of Aging

With age, some of the mechanisms required to maintain organ function are impaired, which results in decreased repair capacity. Among the different biological mechanisms that might account for organ aging, somatic senescence has been proposed as a key contributor. The term senescence applies to irreversible growth arrest with viable cells lacking mitogenic stimuli [10]. Thus, while

Table 2. Modify agents of cell senescence in the elder kidney

Proposed agent	Mechanism
Direct activation of telomerase	Counteracts telomere shortening [12]
Antioxidant	Reduces oxidative free radicals → reduces senescence [21]
Statin	Indirect activation of telomerase Upregulates expression of telomerase and telomere repeat-binding factor [22]
Peroxisome proliferator-activated receptor agonist	Increased expression of Klotho and decreased systemic and renal oxidative stress [23]
Klotho	Antioxidant and anti-inflammatory properties [24, 25]
Calorie restriction	Reduces oxidative free radicals → reduces senescence [17]
Bone marrow	Replaces renal senescent cells with nonsenescent cells [26]
Transplantation of old muscle	Restores regenerative capacity [27]

these cells do not necessarily die, their ability to grow is impaired.

Several mechanisms may contribute to senescence occurring with aging. Telomeres are nucleoproteins consisting of repetitive DNA sequences and specific proteins that are located at the end of all eukaryotic chromosomes. Telomeres and telomerase enzymes are thought to play a role in cell senescence [11]. Telomeres are involved in the control of chromosome stability, genetic integrity, and cell viability. When telomeres are damaged or critically short, their protective function is impaired. Telomere shortening forces human primary cells, including endothelial cells, to stop dividing. The enzyme telomerase counteracts the shortening of telomeres [12]. This enzyme contains a catalytic subunit: telomerase reverse transcriptase (TERT). Introduction of TERT into human cells was shown to extend their life span as well as lengthen telomeres to lengths typical of young cells [13, 14]. Telomere attrition due to repeated loss and the inability of adult human cells to synthesize de novo telomeres due to the lack of telomerase enzyme occurs with aging and may contribute to cellular senescence. Other cellular stressors suggested as mechanisms of senescence with aging include increases in oxygen radicals, fibrogenic mediators, and mitochondrial injury [15, 16]. These mechanisms may cause a shift towards an imbalance in cell repair and proliferation. In the kidney, renal epithelial cell proliferation decreases with aging. At some point, <1% of tubular cells proliferate [17]. This decline in renal epithelial cell proliferation with aging results in the loss of epithelial cells, and hence loss of renal parenchyma [18]. Several genetic, hormonal as well as other mediators increase, and contribute to the cell senescence and decreased capacity of the aging human kidney to cope with abnormal stresses. There is an increase in the cell

cycle regulator gene p16^{INK4A}, as well as other mediators such as cyclooxygenase-1, transforming growth factor- β , and p53 [17].

DNA from human kidneys also demonstrates significant telomere loss with aging. The loss of telomeres and DNA repeats at the end of the chromosome results from a lack of telomerase activity and is usually accompanied by cellular senescence [12]. The *klotho* gene expressed in the kidneys is named after the Greek goddess who spins the thread of life. The *klotho* mouse whose *klotho* gene is mutated is characterized by a very short life span. Overexpression of Klotho was shown to extend the life span in the mouse, suggesting a role for this gene as anti-aging gene [19, 20].

Modifying Cell Senescence in Kidneys of Older Patients

Aging is associated with impaired adaptive and homeostatic mechanisms leading to cellular senescence and death. Research has focused on attempting to identify agents that can modify cell senescence in the aging kidney (table 2). Reactive oxygen species (ROS) have been implicated in aging. Increased generation of ROS stimulates export of TERT from the nucleus into the cytosol. The antioxidant N-acetyl cysteine reduced intracellular ROS formation and delayed export of TERT and its loss of activity, counteracting the shortening of telomeres and thus delaying senescence, which suggests a role for antioxidants in modulating cell senescence [21]. Similarly, statins affect telomere biology. Statins have the ability to cause overexpression of telomere repeat-binding factor [22]. The removal or loss of this factor leads to telomere dysfunction and triggers apoptosis or senescence. Thus,

statins may be beneficial in delaying senescence. Pioglitazone, a peroxisome proliferator-activated receptor- γ agonist that improves insulin-mediated glucose uptake into skeletal muscles, was shown to protect against renal injury in aging. Yang et al. [23] demonstrated that pioglitazone significantly decreased proteinuria, improved creatinine clearance, and significantly ameliorated the development of glomerulosclerosis in aging rats. They suggested that its beneficial actions on the kidney are through increased expression of Klotho and decreased systemic and renal oxidative stress [23].

Klotho has antioxidant and anti-inflammatory properties. The klotho gene is expressed primarily in the kidney (distal convoluted tubules) and the choroid plexus of the brain [19]. Klotho acts as a coreceptor for FGF23 and plays a role in phosphate and vitamin D metabolism. In addition, Klotho is cleaved by ADAM10/17, and the extracellular domain of Klotho is released into the circulation and can act as a hormone to modulate mitochondrial oxidative stress and ameliorate renal injury [24]. Urinary levels of Klotho were shown to be low in several renal disease conditions, including CKD in humans and mice [25] as well as AKI in rats [24], suggesting a potential protective role for Klotho. Whether Klotho has a potential therapeutic role in the aging human kidney remains to be elucidated.

Similarly, studies showed that replacing renal senescent cells with nonsenescent cells [26] and transplantation of old muscle [27] may modify cell senescence in elderly kidneys.

Regeneration following AKI in Older Patients

In AKI, more prolonged disease and less successful functional recovery are noted in older patients. AKI is more prevalent in older individuals, mainly due to two reasons: the increased susceptibility of the old kidney to develop AKI and the diminished repair ability of the aging kidney [28, 29].

The increased susceptibility of the elderly to develop AKI is due to multiple causes: the structural and functional changes in the aging kidney, as previously discussed, leading to diminished perfusion, excessive interventional procedures, avid use of contrast dye and nephrotoxic drugs such as nonsteroidal anti-inflammatory drugs, as well as the multiple comorbidities that accompany aging. On the other hand, aging affects the normal response of the kidney to acute damage. In response to AKI, cell proliferation and tubule repopulation are inad-

equately leading to incomplete recovery. The precise mechanism for such age-related inadequacy remains unclear. In comparison to younger patients, 20–30% of older patients who survive AKI fail to completely recover renal function [17]. Hence, identifying therapeutic methods tailored to AKI in older patients is crucial. In the setting of CKD, renal cell damage may trigger the release of cytokines and other signals that may favor maladaptive pathways leading to myofibroblast transformation and glomerular and tubulointerstitial space fibrosis. Glomerular regeneration may involve the division of parietal epithelial cells, located at the glomerulus urinary pole, to produce progenitors that migrate and replace damaged or lost podocytes [30]. Whether similar processes occur following AKI with regression of fibrosis is not known.

Several factors regulate epithelial cell proliferation and thus modify the aging phenotype and accelerate recovery following an acute insult. Zinc- α_2 glycoprotein expression was demonstrated to increase following an insult to the mouse kidney with a resultant decrease in epithelial proliferation [31]. In a zinc- α_2 glycoprotein knockout rat model, proliferation increases and promotes recovery [31].

Similarly, regeneration of the kidney following ischemia-reperfusion injury in rats was associated with increased levels of mRNA fibrinogen (Fg) α , β and γ [32]. It was further demonstrated that Fg β -derived B β (15–42) peptide administered shortly (1 min) after ischemia reduced reperfusion injury associated with reduced apoptosis and enhanced epithelial cell proliferation 48 h after reperfusion. Taken together, these results suggest a role for Fg β -derived B β (15–42) peptide administration to protect mice from kidney injury induced by ischemia-reperfusion by enhancing epithelial cell proliferation and tissue repair [32].

Following AKI, there is debate as to the source of the cells involved in reconstituting the epithelial cell population [summarized recently in ref. 33, 34]. Potential sources include endogenous surviving epithelial cells, hematopoietic stem cells, or intrarenal stem cells. Bone marrow-derived cells have been shown to engraft minimally in regenerating kidneys following AKI, which suggests that bone marrow-derived cells do not directly repopulate tubules following injury. Cells such as mesenchymal stem cells exert indirect effects to repair injured epithelium through paracrine mechanisms rather than through integration into the kidney parenchyma [35] or through transfer of genetic information to enhance repair [36, 37]. Elegant fate mapping studies by Humphreys et al. [38] demonstrate that fully differentiated epithelial cells that

survive the injury have the capacity to dedifferentiate, proliferate, and differentiate into epithelial cells. These studies, however, did not rule out the possibility that a minority population of stem cells could have differentiated into epithelial cells. Recent studies have identified a population of proximal tubule cells that are vimentin, CD24, and CD33 positive, and thought to be involved in regeneration following AKI [39]. However, these cells are likely not to be responsible for the majority of repair following AKI, but rather repair is more likely to occur from adjacent surviving epithelial cells that have equivalent capacity to repair [40]. In the aging kidney, the proliferative potential of tubular cells declines with chronological age. The high load of senescent cells in the aged kidney contributes to this decreased proliferative capacity.

Conclusion

Aging, as well as kidney disease in the older patients, is on the rise. Both conditions constitute a burden on the health care system. Understanding the mechanisms of aging and the effects that aging has on the kidney structure and function will serve in identifying therapeutic measures that have the potential of ameliorating some of the changes occurring in the kidneys with aging and hopefully help reverse some of the kidney diseases.

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