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Review

Age and frailty: are they related in decline of renal function?

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The chronic kidney disease (CKD) is defined as abnormalities of kidney structure and/or function, present for at least 3 months, with implications for health. Incidence and prevalence differ between countries ranging from 10 to 20%. In the Baltimore longitudinal studies, Lindeman et al. reported the rate of decline in renal function with aging. The average decline in clearance of creatinine (ClCr) was 0.75 ml/min/year. The prevalence of frailty overall among the Cardiovascular Health Study cohort was 7%, but when restricted to patients with CKD, the prevalence of frailty raised to 15%. However, presence of frailty during CKD was associated with about a twofold higher risk for mortality. Because frailty and CKD are associated with age, poor clinical outcomes, falls, disability, hospitalization and mortality, it is important to identify the subjects at high risk and needing a comprehensive care in order to improve outcome for this vulnerable population.

Key words: Renal, Age, Frailty, Elderly

EPIDEMIOLOGY OF RENAL FUNCTION IN ELDERLY

The chronic kidney disease (CKD) is defined as abnormalities of kidney structure and/or function, present for at least 3 months, with implications for health [1]. Incidence and prevalence differ between countries ranging from 10 to 20%. The prevalence of chronic kidney disease (CKD), defined as persistent kidney damage usually marked by albuminuria or reduced glomerular filtration rate (eGFR < 60 ml/min/1.7 m^2), significantly increases with advancing age [2]. CKD was independently associated with mortality regardless of age [3]. The prevalence of CKD in the > 65 years old population, according to the literature, was approximately 44% [4]. Age is a main determinant of eGFR, classified as unmodifiable risk factor, which can also be considered as a 'container' consisting of multiple different and specific physiological mechanisms. These include stiffening of the arteries, widening of arterial Pulse Pressure (PP), endothelial dysfunction and others [5].

MECHANISMS OF RENAL AGING

Aging is a complex process that negatively impacts the development of different systems and their ability to function [6]. Despite the wealth of phenomenological information on renal aging, the underlying molecular mechanisms are not entirely clear and seem to involve several pathways that affect cellular function [7 8]. Chronic inflammation or parainflammation (i.e. response of the immune system to disturbed tissue homeostasis) belongs to these pathways [9], resulting in accumulation of macrophages, lymphocytes, inflammatory (e.g. IL-1, IL-6, TNF-α) and pro-fibrotic factors (e.g. IL-4, IL- 13, TGF-ß, collagen I and IV), that ultimately lead to reactive interstitial fibrosis and declining renal function. In addition, the kidney seems to lose part of its repair ability, due to a decline in the proliferative potential of e.g. proximal tubule cells, enhanced senescence, intensified expression of cell cycle inhibitors (e.g. p21), increased apoptosis and reduced expression of growth factors (e.g. EGF, IGF-1, VEGF). Thereby, minor insults that are

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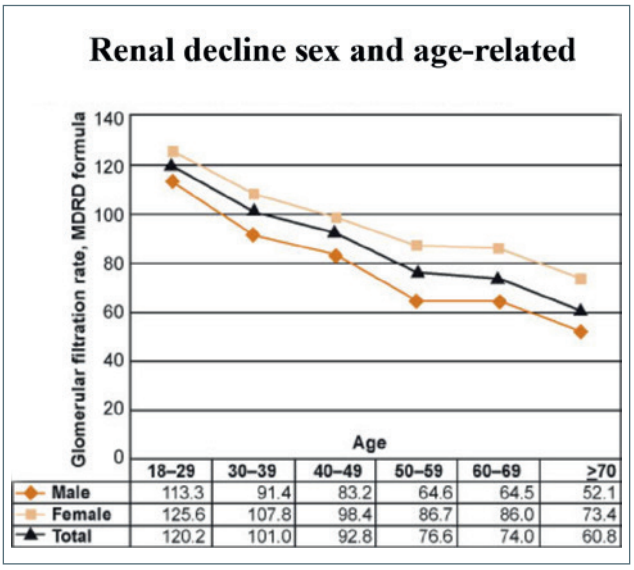
repaired in younger kidney will accumulate and contribute to reduce functional reserve in aged kidney [10]. As almost every organ, the kidney suffers from increasing oxidative stress with aging and a vascular Nitric Oxide (NO) deficiency. The reduced Nitric Oxide Synthase (NOS) activity impairs the control of renal circulation and contributes to changes in glomerular function. Possibly, Advanced Glycation End products (AGEs), the result of glycation, are important mediators of age-related stress, because the decrease in renal function correlates with circulating AGEs levels [11]. In addition, accumulating mitochondrial damages, with disturbed energy homeostasis, have been suggested as drivers of tissue aging.

MORPHOLOGICAL CHANGES OF THE AGING KIDNEY

The kidneys are affected by the aging process, which results in numerous effects on the renal system (Figg. 1-2). Renal mass decreases between the ages of 30 and 80 years, with the steepest decline observed after age 50 [12]. Fat and fibrosis scarring, which may replace some parenchymal tissue, occurs primarily in the renal cortex and affects the nephrons that are important for maximal urine concentration. Even in normal aging kidneys, 30% of the glomeruli are destroyed and display diffuse glomerular sclerosis by age 75 [13] and the remaining glomeruli exhibit impaired filtering ability. The age-related findings on kidney biopsies can be defined by nephrosclerosis, including glomerulosclerosis, tubular atrophy, interstitial fibrosis, and arteriosclerosis. Previous studies had shown an increased proportion of globally sclerotic glomeruli with aging [14]. The glomerulosclerosis, occurring with aging, has an ischemic appearance with intracapsular fibrosis, suggesting a primary vascular origin for the lesions. Some functional glomeruli show ischemic capillary wrinkling of tufts, thickening of basement membranes, and mild intracapillary fibrosis, all of which are precursors for glomerulosclerosis. Over time, shrinkage of the glomerular tufts with sclerosis and collagen deposition filling Bowman's space develops [15]. Besides glomerulosclerosis, increased arteriosclerosis, medial hypertrophy, and arteriolar hyalinosis occur with aging [14].

FUNCTIONAL CHANGES IN RENAL FUNCTION WITH AGING

In the Baltimore longitudinal studies, it has been reported the rate of decline in renal function with aging. The average decline in clearance of creatinine (ClCr) was 0.75 ml/min/year [16]. In adults, the GFR decline per year varies dramatically between studies, ranging from 0.4 to 2.6 ml/min [17]. Fliser et al. [18] suggested that the elderly population was heterogeneous – some having a decline in GFR explained by diseases that complicate aging such as arteriosclerosis with hypertension, whereas in most of healthy adults the decline in GFR is much more modest and not inevitable. Fliser et al. also proposed that the renal functional changes accompanying aging might be the consequence of an altered



	18–29	30–39	40–49	50–59	60–69	>70
Male	113.3	91.4	83.2	64.6	64.5	52.1
Female	125.6	107.8	98.4	86.7	86.0	73.4
Total	120.2	101.0	92.8	76.6	74.0	60.8

Figure 1. Renal decline by sex and by age.

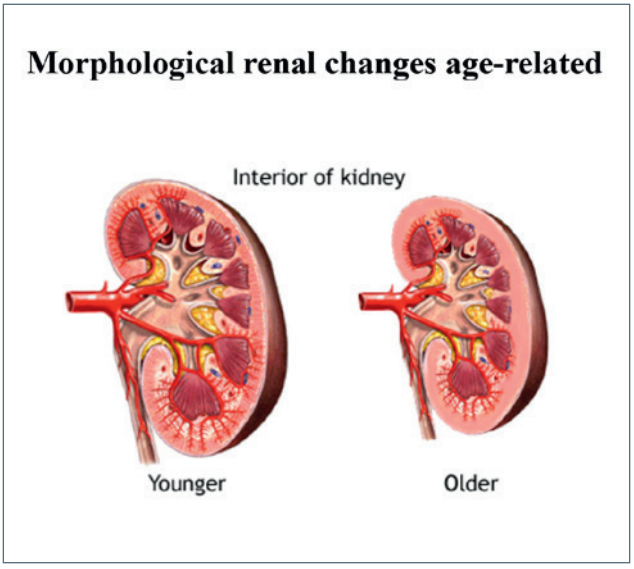


Figure 2. Morphological renal changes age related.

responsiveness to vasodilators and vasoconstrictors [19]. This thesis is based on observations that the filtration fraction increases with aging, due to a disproportionate fall in renal plasma flow relative to GFR. The filtration fraction does not begin to increase up to 60 or 70 years, while the decline in GFR begins at age of 30-40 years. Na^+-handling is altered in the aged kidney, so that proximal reabsorption is enhanced and distal reabsorption reduced, resulting in a narrow range [20] with consequent reduced response to altered Na^+-load. Because sodium is the main determinant of extracellular volume, elderly are at higher risk of volume depletion and salt retention when sodium supply is out of the "normal" range. In addition, there is a reduced activity of the renin-angiotensin-aldosterone system and possibly a partial resistance to atrial natriuretic peptide, both of which contribute to the reduced functional reserve in Na^+-homeostasis. In respect to renal K^+-handling, renal tubular secretory capacity decreases with age, probably due to reduced Na^+/K^+-ATPase activity [20] in the distal nephron and reduced aldosterone levels. The tendencies to dehydration (lower urine flow rate) and metabolic acidosis in elderly contribute to the reduced functional reserve in K^+-homeostasis. Renal concentrating and diluting abilities are reduced, leading to lower maximum urine osmolality, decreased minimum urine flow and worsen free water clearance [21]. Finally, there is also a reduced functional reserve in acid-base homeostasis, with lower renal acid excretion capacity, due to decreased ammonia genesis in the proximal tubule and reduced H^+-ATPase activity in the collecting duct, whereas acid excretion is mostly normal [22]. With aging, renal renin release decreases, leading to lower plasma renin activity and consequently decreased angiotensin-II and aldosterone levels, with consequences for electrolyte and volume homeostasis. By contrast, plasma $1.25(OH)_2D_3$ levels are in the low-normal range in healthy elderly, with plasma $25(OH)D_2$ levels reduced and plasma PTH levels enhanced. This constellation can be interpreted as substrate deficiency for the proximal tubule compensated by enhanced PTH release, stimulating renal $1.25(OH)_2D_3$ formation [23 24]. Plasma erythropoietin levels are mostly normal in healthy elderly and only show reduced levels in anaemic subjects, indicating an impaired responsiveness of renal erythropoietin formation. Finally, renal production of the calcio-phospho regulatory hormone [25] decreases with age. However, several studies have shown that renal-synthesized C-type natriuretic peptide (CNP) is correlated with intrarenal regulation of water and electrolyte homeostasis in kidneys of diabetic rats [26]. Importantly, it has also been reported that urinary CNP serves as a marker for increased intravascular and renal interstitial pressure in an animal model of acute intravascular volume overload [27]. In addition, Segawa et al. [28] and Cannan-Kuhl et al. [29] have demonstrated that CNP inhibits rat mesangial cell proliferation, consistent with antiproliferative properties of CNP in the vasculature [30]. Because abnormal hyperproliferation of mesangial cells is believed to be one of the pathophysiological mechanisms leading to chronic renal failure [31], it is possible that the antiproliferative actions of CNP could play an important role in patients with progressive renal failure [32].

ARTERIAL STIFFNESS AND AGE

Arterial ageing is related to changes in the mechanical and structural properties of the vascular wall, which lead to loss of arterial elasticity and reduced distensibility [33-35]. Arterial stiffness is an important mechanism in the development of age-related renal function decline [36]. The age represents a non-modifiable factor that in healthy adults causes increased arterial stiffness and changes in chromosome replication with telomere shortening [37]. Aging is associated with poorer vascular endothelial function and increased mortality [38-40]. The renal microcirculation of elderly is more vulnerable to the damaging hemodynamic effects of arterial stiffness than in younger people. This could reflect an impaired blood pressure buffering capacity of the vascular wall, caused by arterial stiffening that occurs mainly with advancing age. In CKD, the most common arterial lesions are both occlusive, affecting the intima (atherosclerosis) and remodelling lesions, affecting the media (arteriosclerosis), resulting in an increased arterial stiffness and diameter [41]. Conflicting results have been published about the impact of arterial stiffness on CKD progression. Mitchell et al. [42] demonstrated that central arterial hemodynamic significantly changes from the age of > 60 years, as result of arterial stiffening and, thereby, contributes to increased blood pressure pulsatility. From the age of > 62 years, the correlation between PWV (as indicated as arterial stiffness) and annual change in eGFR becomes stronger [36].

ASSESSMENT OF RENAL FUNCTION IN THE ELDERLY

Creatinine is the endogenous marker widely used for estimation of renal function. The Cockcroft-Gault formula, which estimates ClCr without adjusting body surface area, and the modification of diet in renal disease (MDRD) formula, which estimates GFR adjusted to standard body of the eGFR [43] use the same variables as the MDRD equation but were developed using a different sample of patients. The inclusion of

age and gender as variables is to provide surrogacy for anticipated endogenous creatinine production rate, which inevitably declines with age due to loss of lean body mass [12]. Assessment of GFR by classical 24-h-clearance (using for example inulin or at least creatinine) or by plasma clearance (using e.g. iohexol) is rarely performed, although these are the gold standards. For practical reasons, GFR is often estimated from serum creatinine using certain formulas (e.g. Chronic Kidney Disease Epidemiology Collaboration, CKD- EPI; Cockcroft-Gault, CG; Modification of Diet in Renal Disease, MDRD). Unfortunately, these formulas are not sufficiently validated for the elderly and are afflicted by great variance and uncertainty. One reason is the hyperbolic relationship of serum creatinine with GFR that limits sensitivity, especially when kidney function is still in the upper 50%. A second reason is the dependence of creatinine formation on muscular mass that changes with age and is affected by age-related modifications, like sarcopenia. To this regard, Giordano et al. reported that in older adults with type 2 diabetes, long-term effects of a moderate protein dietary (MPD) regimen are associated with a significant reduction of decline in renal function, proteinuria, low-grade inflammation, and oxidative stress without a change in fat-free mass [44]. A study from 1997 comparing GFR, of healthy people aged 68 ± 7 years with a group of healthy people aged 26 ± 3 years [23] showed that GFR of the elderly was 85% lower in respect to the value of the young group, but still in the physiological range. The newly developed Berlin Initiative Study (BIS) equation (BIS2: creatinine- and cystatin C-based) may provide more precise and accurate tools for estimating GFR in the elderly group. This equation yielded the smallest bias followed by the creatinine-based BIS1 (BIS1: creatinine-based) and Cockcroft–Gault equations. All other equations considerably overestimated GFR. The BIS equations confirmed a high prevalence of persons older than 70 years with a GFR less than 60 mL/min per 1.73 m^2. In Table I we illustrate the bias of existing equations using different statistical parameters. Apart from the BIS2 equation, all other equations had a much larger proportion of false-negatives (wrongly considered %60 mL/min per 1.73 m^2) than false-positives (wrongly considered < 60 mL/min per 1.73 m^2) [45]. Thus, there was a decline with age, without threatening homeostasis.

THE RISK OF END STAGE RENAL DISEASE (ESRD) IN ELDERLY WITH CKD

Elderly patients have become prevalent also in nephrology clinics [46]. This epidemiological finding is critical for three reasons. First, nephrologists represent the main reference of care for patients with overt non-dialysis CKD. Second, the number of elderly patients referred to a nephrologist has significantly grown in the past decade [47]. Third, worldwide patients followed in the nephrology setting are characterized by more advanced renal disease and higher burdens of CVD comorbidities [48]. It is also still unknown whether and how age influences the predictive role of other risk factors for ESRD and death. De Nicola et al. [49] recently reported the modifying effect of age on the competing risk of ESRD *vs* death and on the predictive role of the main risk factors in a cohort of patients with non-dialysis CKD under stable nephrology care. Frail patients undergoing haemodialysis had a 2.6 times higher risk of mortality and 1.4 times higher risk of hospitalization, independently by age, gender, comorbidity and disability, compared with no frail patients [50]. Frailty, measured by the original criteria of the frailty phenotype in a haemodialysis population, was found in all ages with an overall prevalence of 42% [50], compared to the prevalence of 7% in a elderly community-dwelling population [51].

CKD AND PRE-CLINICAL FRAILTY

Experts have proposed various definitions of frailty [52], all of them designed to identify a group of older adults vulnerable to mortality, morbidity, and functional decline in settings of acute stress-stemming from low physiologic reserve. Frailty can precede disability [53]. The Cardiovascular Health Study definition identifies a person as frail if meets three of the following criteria: weight loss, weakness, poor energy or exhaustion, slowness, and low physical activity. For participants identified as frail, the risk of falls and worsening mobility during a period of 3 years was 30% and 50% higher, respectively; the risk of worsening ADL disability and mortality was double that of non-frail participants [51].

Frailty is currently considered as “primary” or “pre-clinical” when the state is not associated directly with a specific disease, or when there is no substantial disability. Accordingly, the presence of three or more of the five criteria is used to identify pre-clinical frailty (unintentional weight loss, exhaustion, low energy expenditure, slowness, and weakness) [53]. The prevalence of frailty overall among the Cardiovascular Health Study cohort was 7%, but when restricted to patients with CKD, the prevalence of frailty raised to 15%. However, presence of frailty during CKD was associated with about a twofold higher risk for mortality. There is a high prevalence of cognitive impairment among older adults with CKD [54]. A potential link between CKD and impaired levels of physical function and cognition may exist simply because CKD is a common disease state, more

Table I. Bias, precision, and accuracy for eGFR equations in aged 70 y or older (from Schaeffner ES, 2012, mod.) [20].

Equation	Mean bias*	SD of difference*	Median bias*	First quartile*	Third quartile*	P_{30} %†	P_{15} %†	Wrongly considered < 60 mL/min per 1.73 m^2, n (5)	Wrongly considered < 60 mL/min per 1.73 m^2, n (5)	Total misclassified n (%)	P value ‡
BIS1	0.11	9.20	0.80	-5.03	6.11	95.1	69.5	27 (17.9)	22 (16.4)	49 (17.2)	NA
Cockcroft-Gault adjusted for BSA	2.74	11.66	2.53	-4.06	9.21	87.4	59.3	29 (19.2)	36 (26.9)	65 (22.8)	0.006
MDRD study	11.21	11.38	11.29	3.85	17.68	70.9	39.3	3 (2.0)	63 (47.0)	66 (23.2)	0.035
CKD-EPI	8.94	10.12	9.69	2.45	15.49	77.9	43.5	4 (2.6)	54 (40.3)	58 (20.4)	0.22
BIS2	0.09	8.06	0.87	-4.40	4.98	96.1	78.9	18 (11.9)	15 (11.2)	33 (11.6)	NA
CysC2§	3.22	10.71	2.05	-3.23	8.61	89.1	63.9	15 (9.9)	28 (20.9)	43 (15.1)	0.041
CysC2§	9.32	9.84	9.22	3.46	14.42	81.4	47.0	4 (2.6)	54 (40.3)	58 (20.4)	0.001

likely to be found in older adults who are in ill-health and therefore also suffering from functional [55] and cognitive limitations. For example, CKD may simply be a marker for the frail phenotype – particularly because no prospective studies have still examined whether incidence of frailty is higher in older adults with CKD.

CKD AND CLINICAL FRAILTY

Frailty is considered "secondary" or "clinical" when it is associated with known comorbidity and/or disability [56]. The characteristics of clinical frailty include not only comorbidity and disability, but also polypharmacy and related adverse drug reactions, hospitalization, health service utilization, age-associated sensory deficits and lack of social support [57]. This condition is associated with higher long-term mortality, both alone and in association with chronic diseases such as chronic heart failure [58]. To this regard it has been reported that the presence of frailty in diabetes subjects strongly influence long-term mortality. Accordingly studies reported long-term mortality was higher in elderly subjects with than in those without COPD [59].

Other results indicate that mortality at the 12-year follow-up was similar in subjects with and without osteoarthritis (OA) [59]. Clinical frailty strongly influences mortality in subjects with OA. However, CKD may be a potential accelerant of decline in physical and cognitive functions through associated anaemia, mineral-bone disease, or inflammation. Anaemia commonly coexists with CKD, a comorbidity that may be particularly detrimental for older adults because its presence has been linked to adverse outcomes including falls, impaired physical function, and cognitive decline [60]. Cross-sectional analyses from the Women's Health and Aging Study II [61] also reported an association between anaemia and poorer scores on tests of executive function and selective attention performance. Disorders of mineral-bone metabolism leading to abnormal bone architecture and fracture may in part explain the relationship between CKD and low physical function. For example, the prevalence of hip fractures among persons with eGFR < 60 ml/min/1.73 m^2 was double that of the general population in NANHES Nutrition Survey III [62]. A complex interplay of hypocalcaemia, hyperphosphataemia, hyperparathyroidism, vitamin D deficiency (both 25-OH and 1,25-OH vitamin D), and metabolic acidosis has been implicated in these processes [63]. Thus, mineral-bone disease associated with CKD leads to increased risk for hip fracture, which in turn is associated with substantial physical disability [64] and could be one important mechanism for the observed indirect correlation between eGFR and physical function. The effect of age on the fate of CKD patients does not represent the only critical issue in contemporary geriatric nephrology research, and in clinical practice as well; attention, in fact, has been recently drawn to the gaps of knowledge on age-related differences in the mechanisms and pathways that contribute to progression to frailty, ESRD and mortality [65]. This information is essential to better delineate the risk profile, and preliminary to the identification of therapeutic goals, in elderly patients. De Nicola et al. [49] found that in the early stages of CKD, the presence of higher proteinuria significantly increased the risk of ESRD in older patients, suggesting that the kidney of elderly is more vulnerable to the 'nephrotoxic' effects of proteinuria due to the greater degree of renal fibrosis and ischemia. CKD has been recognized as an important predictor of adverse health outcomes, including increased risk for cardiovascular disease and mortality, and responsible of drugs toxicity [66]. Persons with CKD

also have reduced health-related quality of life, diminished cognitive function, and a high prevalence of such physical symptoms as fatigue, nausea, and anorexia [67]. The authors found that elderly with CKD were 3 times as likely to be frail as those with normal renal function, association that remained significant after multivariate adjustment for demographic characteristics and comorbidity, as well as such potential mediators as inflammation and subclinical atherosclerosis [68]. Inflammatory factors are associated with both CKD and frailty, and inflammation appeared to partially mediate the association between CKD and frailty [69].

CONCLUSIONS

Renal function is sufficiently preserved in elderly. Most probably, a minimum functional level to maintain homeostasis under "normal" environmental conditions is undercut only in very old people. Thus, renal aging is first of all characterized by a decreasing regulatory range and not insufficiency under regular conditions and behavioural flexibility. As the population of dialysis and pre-dialysis patients is growing, frailty will become an important issue for clinical care. Because frailty and CKD are associated with age, poor clinical outcomes, falls, disability, hospitalization and mortality, it is important to identify the subjects at high risk and needing a comprehensive care in order to improve outcome for this vulnerable population.

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