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ORIGINAL ARTICLE

Diagnosis of Chronic Kidney Disease in the Elderly – A Challenge for the Practitioner

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Abstract: *The recent increase in life expectancy is the main argument for a better understanding of the pathophysiological mechanisms underlying aging. These, once known, can provide possible links to therapies to prevent aging or slow down the process. Normal aging is associated with a progressive decrease in the glomerular filtration rate. Accurate estimation of GFR in the elderly is under the suspicion of multiple errors mainly due to sarcopenia and decreased protein intake. Differentiation between chronic kidney disease and the physiological decline of GFR might be a challenge in clinical practice and this has consequences on the evolution and treatment of the numerous comorbidities of the elderly. The current trend to use non-invasive diagnostic techniques explains the need to identify a serological marker to help differentiate between decreased GFR secondary to kidney aging or the development of chronic kidney disease.*

Keywords: *elderly, normal kidney aging, chronic kidney disease*

INTRODUCTION

Globally, there is a progressive aging of the population.

According to the United Nations Report, 1 in 11 people was over 65 years old in 2019 and it is estimated that in 2050, 1 in 6 people will be this age [1].

The aging process affects the whole body and is characterized by structural changes and functional decline in all organs, leading to an increased incidence of many diseases considered "specific to the elderly". Among these changes, the aging-associated alterations in both structure and function of the kidney are particularly important, having consequences on the evolution and treatment of the numerous comorbidities of the elderly.

Accurate quantification of kidney function in the elderly is difficult, both overestimating and underestimating the glomerular filtration rate (GFR) being possible with currently available serum creatinine-based calculation formulas.

AGING KIDNEY PROCESS

An accurate description of histological changes in the senile kidney, i.e. changes attributed to advanced age per se, is difficult because the elderly usually accumulate important comorbid burdens with impact on the kidney structure and function: diabetes, hypertension, heart failure, etc. Many of the terms that describe physiological changes in the aged kidney superimpose with terms that describe renal pathological processes: nephrosclerosis, tubulointerstitial sclerosis, glomerulosclerosis, arteriosclerosis, etc.

Macroscopically, starting from the 4th decade of age, the kidneys begin to decrease in size and weight progressively, so that around the 7th decade there is a reduction by about 20-30% of kidney weight compared to the age of 40 years [2]; in the elderly without kidney disease, the decrease in kidney size is symmetrical. Also, with age, the kidney's cortex becomes thinner and rougher, the number and size of benign cysts

increases, and the pelvis is enlarged with more fatty infiltration. The scarring is more advanced when associated with aortic and renal atherosclerosis (Figures 1 – 5) [3].

Microscopically, starting with the 5th decade of life, there is a progressive decrease in the total number of nephrons due to sclerosis of all nephron compartments [3]: glomerulosclerosis, tubulointerstitial sclerosis, and arteriosclerosis.

The prevalence of glomerulosclerosis increased from 25% in the 3rd decade of life to 82% in the 8th decade [4], the main cause being arteriosclerosis of the small intrarenal arteries.

Figure 1: 87 years old male: granular surface with increased scarring

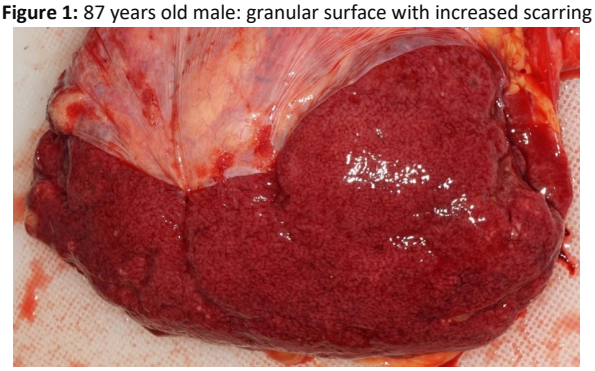


Figure 2: Same case, yellow arrows: small stones, thinning of the cortex

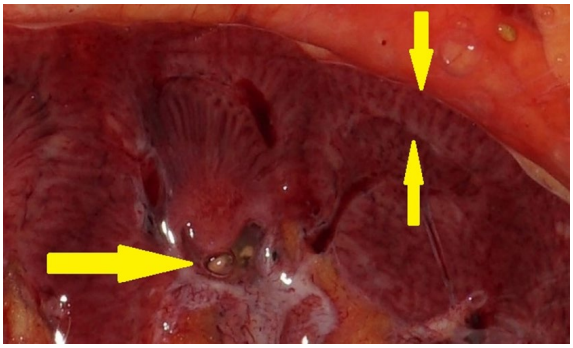


Figure 3: Same case, yellow arrows: glomerulosclerosis (10X HE)

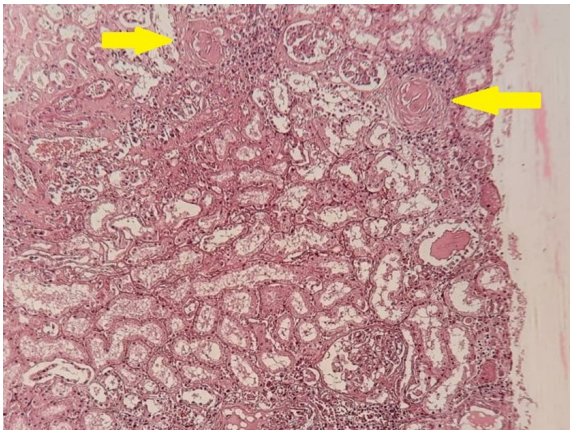


Figure 4: Same case, yellow arrows: arterial wall thickening (10X HE)

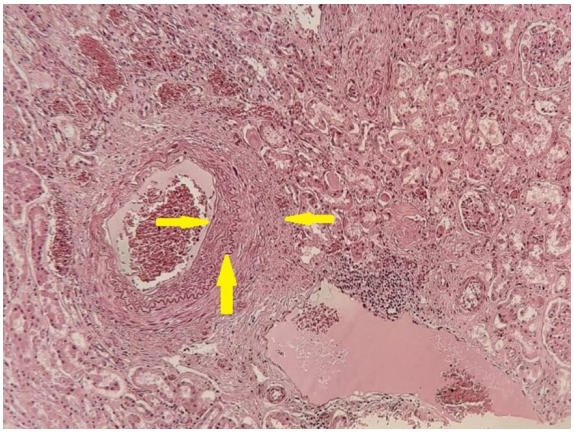
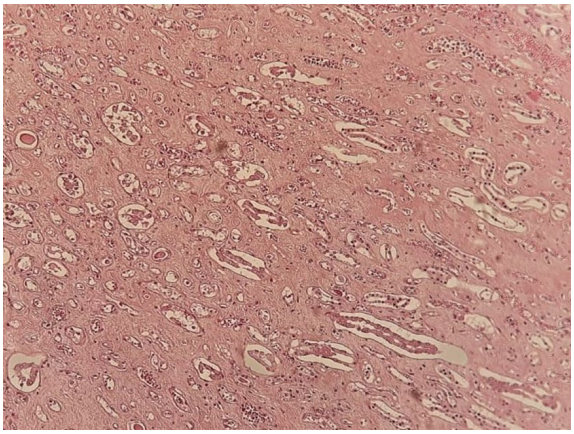


Figure 5: Same case: interstitial sclerosis (10X HE)



The hallmark of the functional decline of the senile kidney is a progressive decrease in the glomerular filtration rate (GFR) [5]. The decline in GFR begins around the 4th decade of life; between the 8th and 9th decades, the GFR is over 45% lower than at the age of 40 [3,6].

ESTIMATED GLOMERULAR FILTRATION RATE (eGFR) IN ELDERLY

There is no consensus regarding the optimal equation for the estimation of GFR in the elderly. Formulas used in clinical practice in adults – MDRD (Modification of Diet in Renal Disease, CKD-EPI (Chronic Kidney Disease – Epidemiology Collaboration), Cockroft-Gault are all based on serum creatinine levels and they have not been all validated for individuals older than 70 years.

Creatinine-based equations for GFR estimation have several drawbacks in older individuals [7]. Due to age-associated sarcopenia, there is a reduced release of creatinine from the muscles, therefore also a reduced urinary excretion of creatinine [8]. In elderly diabetics, especially in the late-elderly group (75 years or older), it has been noted a more decreased

serum creatinine when compared with non-diabetics and this observation was explained by the increased loss of muscle mass promoted by diabetes [9]. Also, the elderly tend to have a reduced intake of proteins and a decreased basal metabolism, therefore, they have supplementary causes for the reduced production of creatinine [10]. Increased metabolism of creatinine by intestinal microorganisms may be an additional cause for reduced levels of serum creatinine, as there are proven age-related alterations of gut microbiota [11]. Formulas using the patient's weight besides serum creatinine give more errors due to increased fat percentage in the organism of the elderly. Several researchers had concluded that both MDRD [12] and CKD-EPI [13] formulas tend to overestimate GFR in the elderly, while Cockroft Gault's [14] formula underestimates it [15,16].

Serum creatinine alone is often used in clinical practice not especially for estimation of GFR, but for monitoring the patient during treatment with a potential nephrotoxic agent (aminoglycosides for example) or a potential ischemic renal insult (cardiac surgery for example). Besides the fact that this conduct is not correct due to the late and modest increase of serum creatinine level compared to the moment and degree of kidney insult, in the elderly, it is a source of supplementary severe misjudgments. The elderly have often lower basal serum creatinine and during an injury renal process, an increase of serum creatinine remains in the range of the normal values of the laboratory and this result may be misinterpreted as a stable state, i.e. no iatrogenic. Moreover, the creatinine increase may be blunted by intensive hydration of the patient applied to minimize the kidney insult.

Formulas based on both serum creatinine and serum cystatin C have been proposed to overcome the disadvantages of formulas based only on creatinine values [17]. Nevertheless, serum cystatin C is influenced not only by kidney function, but also by several diseases often present in the elderly, such as atherosclerosis, inflammatory estates, or obesity [18,19].

Several alternative equations have been developed for older individuals. The HUGE formula (Hematocrit Urea GEnder) was developed in 2011 by a group of researchers from Spain to differentiate patients without CKD from those with CKD [20]; this formula was validated in some studies [21,22].

L = 2.505458 - (0.264418 x hematocrit) + (0.111800 x blood urea); 1.383960 is added for the male patient. For L <0, CKD is excluded; for L> 0, it is classified as CKD.

In 2012, the Berlin Initiative Study (BIS) introduced two new formulas based on serum creatinine and serum creatinine plus serum cystatin C, respectively, for estimating GFR in people over 70 years of age [23].

BIS 1: eGFR = 3736 x serum creatinine-0.87 x age-0.95; in women, the result is multiplied by 0.82.

BIS 2: eGFR = 767 x cystatin C-0.61 x serum creatinine-0.40 x age-0.57; in women, the result is multiplied by 0.87.

Although these formulas have been validated in some studies, there are no large trials to conclude their superior performance, therefore meanwhile guidelines recommend using the same equation as in the general adult population.

NORMAL KIDNEY AGING VERSUS CKD IN ELDERLY

Reported data on CKD prevalence in the elderly is impressive. A highly cited source in the literature is a meta-analysis performed by Hills and collab. which comprises more than 100 reports from all continents; according to this meta-analysis, the prevalence of CKD in all stages in the general population is 13.4% (11,7-15.1%), but increases to 27.6% (range 26.7-28.5%) in the 6th decade and 34.3% (31.9-36.7%) in the 7th decade of life. The same source also revealed increased CKD stage 3-5 in the elderly: from 10.6% in the general population (9.2-12.2%) to 11.3% (8.1-14.5%) in the 6^{th} decade and respectively to 27.9% (16.4-39.3%) in the 7^{th} decade [24]. Nevertheless, a large proportion of the geriatric population meets the KDIGO criteria for CKD even without markers of renal impairment [25,26]. Regardless of the formulas utilized to estimate GFR, an important question needs to get answered in the face of an older patient with abnormal GFR and no markers of kidney disease. Is it CKD without markers of kidney disease or is it normal kidney aging? Several reasons require a response to this question. Establishing a diagnosis of CKD imposes close monitoring of the patient and adequate preparation for conservative or dialysis treatment. Most of the patients aged >65 years have estimated GFR between 45-60 mL/min/1.73m^2; older patients with estimated GFR between 45-60 mL/min/1.73m^2 have, in comparison with younger adults, decreased risk to progress to end-stage renal disease (ESRD), but increased risk to die from other diseases until they reach ESRD [27,28]. Close nephrological monitoring of all these patients would be a significant burden for physicians, and also for the health systems. On the other hand, CKD, even oligosymptomatic, is associated from early stages with increased risk for cardiovascular events and cardiovascular mortality; specific complications of CKD, such as acidosis or increased parathormone (PTH) have early onset and need to be controlled.

There are several subtle clues allowing the differentiation between the physiologic decrease of GFR and CKD (Table 1).

Serum urea and creatinine increase late in the course of CKD in all patients, but especially in elderly patients. Low serum creatinine levels are observed due to decreased basal

metabolism, reduced protein intake, and sarcopenia [3], therefore CKD may be present with normal values of serum creatinine in the elderly. However, the aging kidney excretes increased amounts of urea, due to the reduced density of urea channels in the collecting tubes [29]; a normal serum urea level is associated with normal aging [15].

Table 1: CKD versus normal kidney aging

	CKD	***Aging kidney***
Nitrogen waste products in the blood	Increased	Normal
Albuminuria	Present	Absent
Anemia	Present (erythropoietin deficiency)	May be present (nutritional anemia)
Acid-base balance	Metabolic acidosis	Normal
Ca-P metabolism	Hypocalcemia decreased active vitamin D, increased PTH	Possible hypocalcemia, normal PTH, normal active vitamin D

No anemia should be present as in healthy older populations erythropoietin (EPO) production is normal or even increased secondary to increased erythrocyte turnover, increased EPO resistance, or as a response to occult digestive blood losses [30,31]. Nevertheless, in clinical practice, the elderly have often nutritional mild/moderate anemia that may be misinterpreted as CKD-associated anemia. Reduced secretion of EPO in CKD is associated with normocytic and normochromic anemia, while nutritional anemia is often hypochromic and microcytic [32], but they may coexist.

No abnormalities of mineral metabolism are present in healthy older individuals. Renal tubular excretion of calcium, magnesium, and phosphorus is not altered in healthy elderly [5,33]. The elderly are prone to hypomagnesemia, but this seems to be mainly due to reduced dietary intake, decreased intestinal absorption of magnesium, and/or laxative abuse [5]. Although the elderly present more often with mild hypocalcemia, it occurs mainly secondary to native vitamin D deficiency through reduced sun exposure or decreased skin synthesis of vitamin D [34]. In contrast with CKD, there is no deficiency of active vitamin D, nor an increased synthesis of parathormone in healthy elderly.

Under basal conditions, the kidneys of the elderly have a normal capacity for the excretion of acids and the acid-base balance does not undergo significant changes even with a normal- or hyper-protein diet [35]. However, the renal reserve of the elderly is reduced and a rapidly installed high acid load may be difficult to be compensated by the senile kidney; the elderly are highly vulnerable to the side effects of acute metabolic acidosis (uncontrolled diabetes, sepsis, acute kidney injury).

On the other hand, the presence of albuminuria is a strong argument for CKD even if the patient has other comorbidities that may explain this finding (systemic atherosclerosis, diabetes, cardiac failure). Albuminuria is associated with an increased risk of progression of CKD [36], therefore applying antiproteinuric measures might have the same benefits in the elderly as in younger adults, i.e., attenuating the progression of CKD and reducing cardiovascular events [37]. Nevertheless, overzealous administration of RAAS inhibitors in the elderly is associated with an increased risk of side effects (hypotension, hyperkaliemia, acute kidney injury) in the presence of reduced GFR and systemic atherosclerosis or other comorbidities; another reason why these drugs are no longer needed in elderly without proteinuria is the fact that they become useless, not having time to install their renoprotective effect over time [38,39]. The elderly are prone to hyperkaliemia even in the absence of reduced GFR due to the low sensitivity of distal tubules to aldosterone [31,40].

Taking into account that the elderly have a higher risk of death due to various complications than to progress to ESRD, there is a need to assess individual risk for these outcomes to analyze treatment options and make early plans for conservative treatment (diet, prevention, and control of uremic syndrome with medication) or renal replacement therapy. CKD has an extremely heterogeneous presentation in the elderly; between an independent full-functioning person without cognitive impairment and without major comorbidities at one pole to a frail, immobilized in-bed individual with severe cognitive dysfunction, multiple disabling comorbidities and total dependence for medical care at the other pole, there are numerous clinical pictures. One such equation was proposed by Tangri et al in 2011 who developed the Kidney Failure Risk Equation (KFRE) using variables like age, sex, estimated GFR, albuminuria, serum calcium, serum phosphate, serum bicarbonate, and serum albumin to predict progression toward ESRD after 1, 3 and 5 years respectively for patients with CKD stages 3 to 5 [41]; a variant using only 4 variables (age, sex, estimated GFR and albuminuria) may be used, but the results offer less accuracy [41]. This model has not been designed especially for older individuals, but it has been validated both for patients < 65 years and those above this age and for various races [42,43]. Calculation of this score is

available on the internet at http://www.qxmd.com/Kidney-Failure-Risk-Equation. KFRE is recommended by European Renal Best Practice Group to be used in elderly with an estimated GFR < 45 mL/min/1.73 m^2 to assess progress toward ESRD [44]. Nevertheless, a lot of old individuals are placed in the range of GFR between 45-60mL/min/1.73 m^2 and have no markers of kidney disease (albuminuria) [45]; there are no available validated prediction models for this situation and members of European Renal Best Practice Group opine for the urgent need of such prediction models.

Regarding the prediction of death, in the literature there are numerous scores specially designated for the old population and most of them also include, besides demographic variables (age, gender) and comorbidities (heart failure, diabetes, active neoplasia, anemia, history of stroke, chronic obstructive pulmonary disease, etc.), a marker of kidney dysfunction such as estimated GFR or urinary albumin/creatinine ratio [46-49]. These models estimate the risk of death at periods ranging from 3 months to 5 years. The European Good Practice Guideline recommends the use of the Bansal score in current practice for assessing the risk of mortality of non-fragile, un-institutionalized elderly people with CKD >stage 3b [44,47]; this score uses 9 variables - age, sex, GERD, urinary albumin/ creatinine ratio, smoking, diabetes, heart failure, history of stroke; according to this predictive model, the 5-year mortality varies between 3.8% for individuals with lower scores to 83.6% for individuals with all 9 items reached. Nevertheless, again, none of these models took into analysis the particular situation of individuals with normal kidney aging, i.e. those patients without markers of kidney damage and GFR between 45-60 mL/min/1.73m^2. We found in the literature just one publication, that of Van Pottelbergh and collab. who analyzed mortality of very old (>85 years) individuals with GFR> 60 mL/min versus those with GFR between 45-60 mL/min [50]. According to the authors of this paper, the combination of the baseline estimated GFR and the estimated GFR slope over 3 years can be used to assess the risk of death; in the subgroup of patients having estimated baseline GFR between 45-60 mL/min only those with a GFR decrease ≥ 5 mL/min/year had an increased risk of death, while among patients with baseline GFR > 60 mL/min, a decrease of ≥ 3mL/min/year was associated with increased risk of death. The same authors explained that these changes are a reflection of cardiovascular damage. Also, the authors share the opinion of a lot of others those older adults with GFR between 45-60 mL/min should not be classified as moderate stage 3 CKD.

CONCLUSIONS

Aging associates the functional decline of all tissues and organs secondary to degenerative structural changes. Normal kidney aging is a complex process that is difficult to be differentiated in clinical practice from chronic kidney disease with contemporary available criteria; both share the reduced glomerular filtration rate as the main feature. Nevertheless, it is important to make this differentiation.

Establishing a diagnosis of CKD imposes periodic nephrology consultation for monitoring the progression of the disease, treatment of complications, early planning of conservative or dialysis treatment, and also adjustment of treatment of multiple comorbidities of the elderly. CKD has multiple complications and requires often interdisciplinary care: cardiologists, neurologists, psychiatrists, nutritionists, etc. On the other hand, proving that reduced GFR is only a sign of normal aging and that there are no markers of kidney damage allows gerontologists to provide holistic care for slowing the aging process and minimizing the incidence of high-risk diseases in the elderly.

Thus, misclassifying an elderly person as a patient with CKD involves an unnecessary psychological burden for the patient and his family, as well as unnecessary medical care and increased financial expenses.

Conflicts of interest and sources of funding
The authors declare no conflict of interest.

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Authors' contribution
Conceptualization, D.R., C.D., I.A.V., G.E.L.; methodology, A.L.C., R.F.T.; software, M.O.D.L.; investigation, I.A.V., D.R., C.D.; writing—original draft preparation, A.L.C., F.P.; writing—review and editing, S.I., I.A.V.; supervision, A.L.C., D.I.
All authors have read and agreed to the published version of the manuscript.

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