Aging Kidney: Vascular Characteristics and Assessment

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10.1 The Aging Kidney: Anatomical and Functional Modifications

Renal aging is a multifactorial process where gender, race, and genetic background and several key mediators such as chronic inflammation, oxidative stress, the renin–angiotensin–aldosterone system, impairment in kidney repair capacities, and background cardiovascular disease play a significant role [1]. Features of the aging kidney include macroscopic and microscopic changes and important functional adaptations, none of which is pathognomonic of aging. The principal anatomical modification is a gradual renal mass reduction that is more pronounced in the renal cortex than in the medulla [2, 3]. From a microscopic point of view, the aging kidney displays glomerular, tubular–interstitial, and vascular changes.

10.1.1 Glomerular Changes

The number of functioning glomeruli decreases during lifetime, while the proportion of hyaline and sclerotic glomeruli increases from 1 % in the young adult to 20–30 % in the 80-year-old adult (Fig. 10.1) [4]. In response to the reduced number

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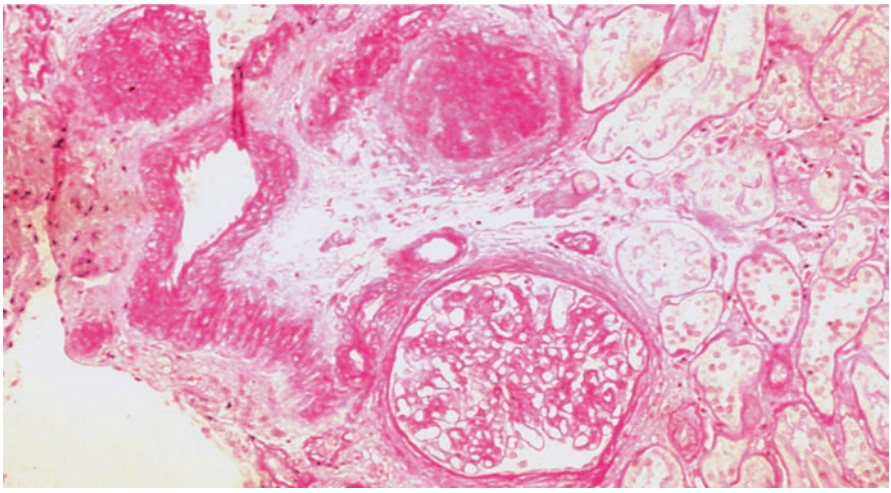

Fig. 10.1 Sclerotic glomeruli in the aging kidney

of functioning glomeruli, the aging kidney is characterized by a hyperfiltering condition with an increase in glomerular plasma flow and intracapillary pressure. However, this adaptation mechanism may accelerate glomerulosclerosis in the long term because it raises intraglomerular pressure [2, 5, 6]. Glomerular basement membrane thickening is another typical feature of the aging glomeruli [3] as it is a mesangial expansion [7]. Glomerulosclerosis prevails in the cortical zone and determines a complete atrophy of the glomerulus, while direct shunts between afferent and efferent arterioles bypass the glomerular tuft in juxtamedullary nephrons [8]. Probably, this is the explanation for the flow preservation in the medulla of the aging kidney.

10.1.2 Tubulointerstitial Changes

As described for glomeruli, the overall number of tubules decreases with age [9], the proximal tubular length is also markedly reduced, while the distal tubules and the collecting duct develop more diverticula that may give rise to form simple renal cysts [4, 10]. Tubular dilatation may be accompanied by accumulation of hyaline material and basement membrane thickening. When extended, this process may lead to a sort of "thyroidization" of the kidney, a common feature in end-stage kidney disease [9]. Expanded interstitial volume, infiltration of mononuclear cells, and diffuse areas of fibrosis are all hallmarks of the aging kidney [11]. Alterations in tubular function go along with anatomical involvement, particularly in renal aging, and decrease the capacity of diluting and concentrating urine [12, 13]. Enhanced proximal sodium reabsorption coupled to reduced distal fractional reabsorption allows maintenance of a normal sodium balance under steady-state conditions in the elderly [14]. However, this functional resetting limits the ability to conserve sodium

in response to low-salt intake and makes elderly people predisposed to volume depletion and acute kidney injury [15]. Inadequate activation of the renin–angiotensin system and reduced aldosterone secretion (hyporeninemic hypoaldosteronism) play a leading role into this phenomenon [16] as well as in nocturnal natriuresis, another frequent alteration in old people [17]. On the other hand, aged individuals display also a relative inability to excrete sodium excess in response to salt load, a multifactorial alteration predisposing to salt retention, hypertension, and cardiovascular congestion. Resistance to the natriuretic effect of atrial natriuretic peptide is a key step into this process [18]. Alterations in tubular handling of electrolytes extend to potassium. Due to tubular atrophy and tubular–interstitial scarring, Na–K ATPase activity is reduced in the elderly, resulting in a high risk for hyperkalemia. Reduction in GFR, hyporeninemic hypoaldosteronism, dehydration, and metabolic acidosis all enhance the tendency to hyperkalemia in the elderly, and the administration of potassium-sparing drugs may precipitate serious clinical events in individuals harboring these risk factors [19]. Even though the renal regulation of acid–base balance is globally conserved in the aging kidney [20], the capacity of generating ammonia is clearly impaired [21]. Elderly subjects are more prone than young individuals to develop acidosis in response to acid load (such as after a high-protein meal or in stress conditions which activate proteolysis) mainly because of the incapacity to increase ammonia and H+ synthesis [22–24]. Impaired proton pump activity in the cortical collecting duct is a critical element in the deranged response to acid load in the elderly [21, 25]. Renal-dependent metabolic acidosis has been implicated in a constellation of alterations in the elderly including hypercalciuria, decreased citrate excretion, enhanced protein catabolism, muscle wasting, bone dissolution, cardiomyopathy, and progression of CKD [26].

10.1.3 Vascular Changes

Structural changes in renal vasculature include intimal and medial hypertrophy, arteriolosclerosis, and overt atherosclerotic lesions [27]. Increased irregularity and tortuosity of pre-glomerular vessels, direct shunts between afferent and efferent vessels (see above), wall thickening and narrowing of the vascular lumen of afferent arterioles [28], and an alteration mainly depending on vascular smooth muscle cell proliferation are observed [29]. In addition, micro-infarctions triggered by cholesterol emboli are often observed along with atherosclerosis of the aorta and renal arteries in elderly patients with diabetes and hypertension. Interlobular arteries in the elderly show fibro-intimal hyperplasia [27], a feature typically observed in patients with chronic hypertension regardless of age.

10.1.4 Functional Changes

Renal blood flow (RBF) decreases with age, falling from 600 ml/min/1.73 m^2 in the young adult to 300 ml/min/1.73 m^2 by the age of 80 [30, 31]. This decrease is due

to both a reduction in renal mass and a progressive reduction in mean blood flow per unit of tissue mass. The decrease in blood perfusion seems to be mainly due to organic abnormalities of intrarenal vessels but also to an impairment of functional vasomotility [31, 32]. GFR decreases less than RBF, so that filtration fraction calculated as [GFR/RBF-FF]- increases [8]. This phenomenon may be due to two possible mechanisms: (1) hyperfiltration of functioning glomeruli due to an efferent arteriole vasoconstriction greater than the afferent one, with a consequent increase in intraglomerular pressure [37], and (2) RBF decrease limited to the cortex, so that medullary flow relatively rises [30–32, 34].

10.1.5 Renal Autoregulation in the Elderly

In healthy subjects, the kidney maintains a constant RBF and GFR regardless of renal perfusion pressure (RPP) over a defined range (80–180 mmHg). This is possible, thanks to intrarenal autoregulation, mediated by myogenic control of arteriolar tone and tubuloglomerular feedback (TGF). The first one consists of changes in the afferent arteriolar tone—vasoconstriction or vasodilation—[35], independently of the local nervous system [36]. This phenomenon is probably mediated by stretch receptors in response to modifications of perfusion pressure [36]. Tubuloglomerular feedback (TGF) is mediated by specialized cells in the macula densa, a region of the thick ascending limb of the loop of Henle adjacent to the glomerular vascular pole. These cells sense changes in the tubular flow, probably through chloride delivery, directly modified by GFR and RBF changes [37]. Via afferent arteriolar resistance, TGF modifies RBF and GFR and consequently normalizes tubular flow. The primary mediators of TGF feedback are not completely understood. Certain studies propose angiotensin II as the main mediator, but it has been demonstrated that it acts only as sensitivity modulator of the feedback response [38]. In fact, angiotensin II modulates TGF activity on the afferent arteriole and directly increases the efferent arteriole tone, with a consequent increase in both glomerular capillary pressure and in filtration fraction when GFR is reduced [39, 40]. Other vasoactive substances like prostaglandins, endothelin, and various endothelium-derived factors modulate autoregulation mechanisms. These autacoids induce variations on GFR and RBF by acting on afferent and efferent arteriole tone, but they also influence other renal functions such as tubular absorption and excretory activity.

10.1.6 Renal Adaptation Capacity During Stress Conditions in the Aging Kidney

The vulnerability of the aging kidney, which manifests itself in the presence of pathological conditions or administration of drugs normally tolerated by the young, is mainly due to an enhanced response to vasoconstrictive stimuli. This hemodynamic reaction can also occur in stressful situations of everyday life such as physical exercise [41]. This tendency may be secondary to the reduction of renal autacoid

modulatory capacity, particularly at the vasodilating prostaglandin level. In our research, we demonstrate that, in the healthy elderly, the renal response to adrenergic activation by mental stress is characterized by a prolonged and pronounced vasoconstriction, due to the lack of prostaglandin modulation of vasoconstrictor factors' activity (Figs. 10.2 and 10.3) [42]. This can explain the greater vulnerability of the aging kidney when NSAIDs are administered, particularly when vasoconstrictive factors, such as during hypotension, hemorrhage, or congestive heart failure, are activated [42].

10.2 Assessment of GFR

Assessment of glomerular filtration ratio (GFR) in elderly people is essential for risk stratification (global, preoperative, etc.), for the use of diagnostic imaging using contrast agents, and for establishing the correct dose of antibiotics and other kidney-excreted drugs.

The gold standard for the evaluation of GFR is inulin clearance, an invasive technique clearly unsuitable for clinical use. Levels of serum creatinine are a poor indicator of renal function in the elderly, since the combination of a reduced muscle mass and physical inactivity maintain levels of serum creatinine normal even for a GFR reduced by more than 50 %. Estimation of GFR is calculated by mathematical formulas which give a rapid, but often imprecise, estimate. Furthermore different formulas present varying degrees of accuracy according to the population considered. In this commentary, our aim is to illustrate the different formulas available, including the new BIS-1 and BIS-2, and offer clinicians a practical guide.

10.2.1 Cockcroft–Gault Equation

This equation generally overestimates renal function because it represents an estimation of creatinine clearance, i.e., the actual filtrate plus tubular secretion of creatinine [43]. Compared to the measurement of creatinine clearance, it presents the advantage of not requiring the measurement of urinary excretion of creatinine. The equation is based on serum creatinine, age, weight, and a corrective index for the female sex. The results are expressed in mL/min, so data on height is required to normalize the value to body surface area. In the original paper, 249 subjects were enrolled, of which 59 aged 70 years or more, with an average creatinine clearance inferior to 40 mL/min. The equation presents two flaws: the tendency to underestimate in advanced age (probably because the few old subjects enrolled in the original study had a reduced muscle mass and therefore produced less creatinine) and to overestimate in case of overweight/obesity or edema. This is due to the fact that in the equation, weight is used as a proxy of muscle mass and therefore of creatinine generation; adipose tissue however does not generate creatinine [44]. One possible solution is to use the ideal, rather than the real, weight [45], but today there are poor indications to use this equation.

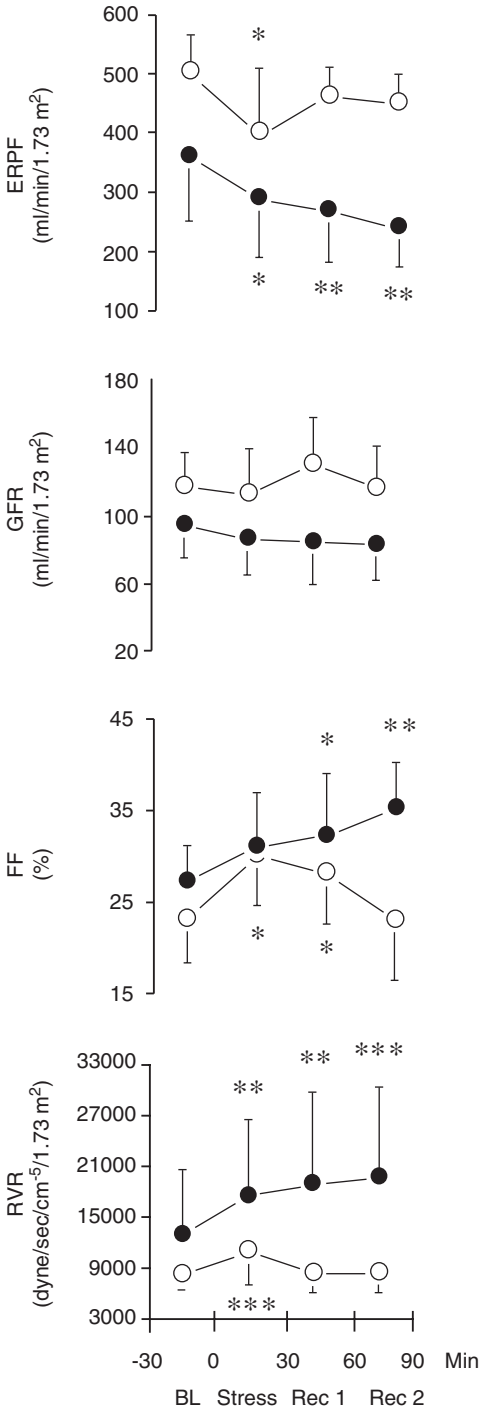

Fig. 10.2 Effects of mental stress on renal hemodynamics (mean – SD). ● Elderly ($n = 8$), ○ young ($n = 8$). *$P < .05$, **$P < .01$, and ***$P < .001$ vs. baseline (least significant difference test, ANOVA). *FF* filtration fraction, *RVR* renal vascular resistance. In the elderly, renal vasoconstriction during and after blood pressure increase determined by mental stress is more pronged and pronounced than in the young (From Castellani et al. [42])

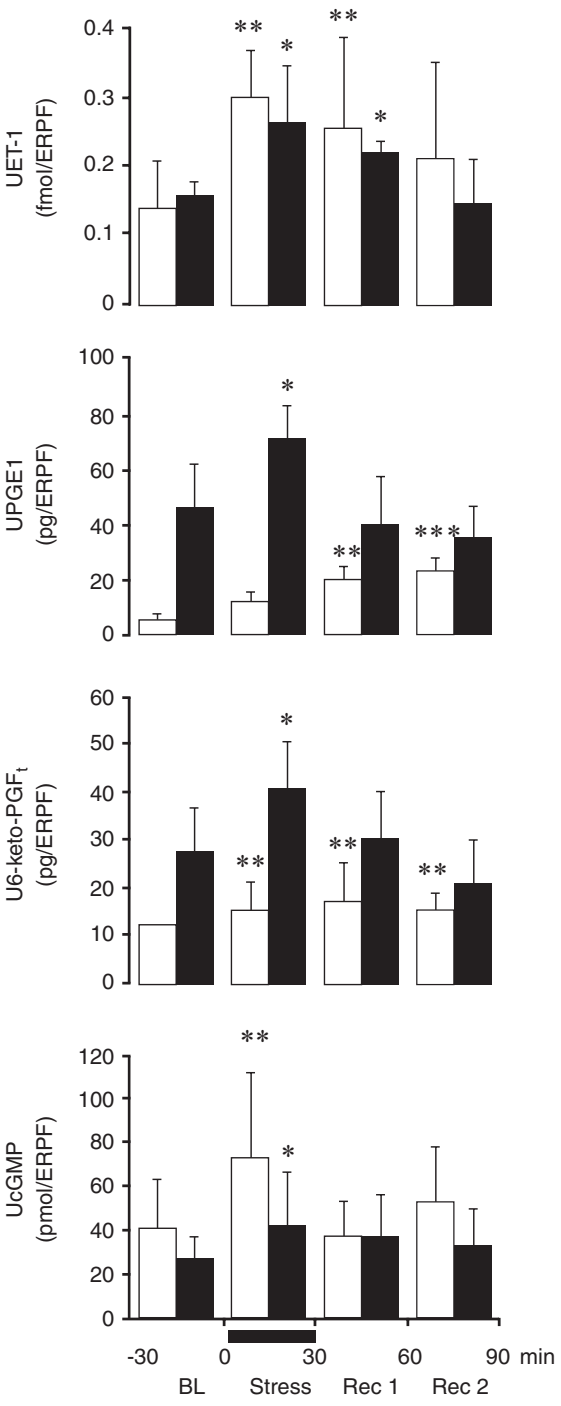

Fig. 10.3 Effects of mental stress on UET-1, UPGE2, 6-keto-PGFm, and UcGMP (mean + SD). ■ Elderly ($n = 8$), □ young ($n = 8$). *P <.05, **P <.01, and ***P <.001 vs. baseline (least significant difference test, ANOVA). In the elderly subjects, the vasodilating prostaglandins increased only during mental stress, while in the younger subjects, the two urinary vasodilating PGs had risen progressively from the start of mental stress application to the end of the experiment, probably for counterbalancing ET-1 increase (From Castellani et al. [42])

10.2.2 MDRD Equation

The four-variable MDRD equation (by the Modification of Diet in Renal Disease (MDRD) study group) is based on creatinine blood levels, age, sex, and ethnicity [46]. The original version included serum urea nitrogen and albumin concentration but was later simplified; in 2006 it was recalculated for use with standardized serum creatinine assay; [47] results are provided directly in mL/min × 1.73 m^2. It has been studied measuring the relationship between creatinine blood levels and GFR measured with radioisotopic techniques in adults with chronic renal failure. The original equation was validated in a population with an average age of 51 years; persons aged 65 years or more represented 22 % of the sample; even in successive validations in larger populations, elder individuals were poorly represented [48]. The main defect of the equation is the lack of validation for estimated normal-high filtrates. This is because the MDRD study did not include healthy individuals; therefore, there is a paucity of data for GFR >60 mL/min × 1.73 m^2 [49]. Other studies have highlighted possible errors in specific subgroups of patients, such as kidney transplant recipients [50], diabetics [51], or in regions outside North America, Europe, or Australia (specific adaptations have been developed in Chinese [52] and Japanese [53] population).

10.2.3 CKD-EPI Equations

The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) aimed at developing more accurate equations for GFR estimated as higher than 60 mL/min/1.73 m^2. This new formula, known as CKD-EPI, pooled information from three large databases of 12,000 subjects, with and without renal disease, using as a reference test iothalamate clearance [54]. The average ages in the development and in the external validation study were, respectively, 47 and 50 years (subjects aged 65 years or more, 13 % and 15 %, respectively). The variables adopted by the CKD-EPI were the same as in the MDRD equation (creatinine expressed by standardized assay). The CKD-EPI equation has a lower bias for the estimation of GFR >60 mL/min/1.73 m^2, with important repercussions on public health and clinical practice: the prevalence of chronic kidney disease, especially among women and Caucasians, is reduced but remains high among the elderly [55]. The new equation however cannot overcome the principal limits of serum creatinine as an endogenous marker of glomerular filtration; indeed all creatinine-based equations should be used with caution in subjects with an altered generation and/or secretion of creatinine: subjects with a reduced muscle mass (limb amputations, cachexia, sarcopenia, muscular dystrophy), athletes with an increased muscle mass, drugs which modify creatinine secretion, etc.). For a few years now, there has been a growing interest in cystatin C (CysC), as a possible substitute for creatinine as a marker of GFR. CysC satisfies the ideal marker criteria: endogenous production at a constant rate, freely filtrated by the glomerulus,

tubular catabolism, and no extrarenal elimination. Furthermore CysC depends less on muscle mass compared to creatinine. However serum CysC levels could be altered, and therefore unreliable, in the presence of systemic infections [56] and thyroid dysfunction [57] and during steroidal therapies [58]. The effects of smoking, obesity, and age still need to be clarified [59]. Issues such as dosage method standardization, definition of a range of normal values, and high costs need to be solved. In 2012, the CKD-EPI group developed two new equations for GFR estimation: one equation uses CysC, age, sex, and ethnicity and the other combines CysC and creatinine with age, sex, and ethnicity [60]. The sample included over 5000 subjects, persons aged 65 years or more were 13 % and 21 % of the populations, respectively, in the development and validation group. The equation that combines creatinine and CysC resulted in a more accurate GFR estimation across the whole range of values, even in specific subgroups, such as persons with a BMI lower than 20 kg/m^2, in which creatinine-based formulas tend to underestimate GFR. Furthermore this equation allows a more correct classification of subjects with GFR values in the 45 and 60 mL/min/1.73 m^2 range, identifying those not affected by renal failure. Cohort studies and meta-analysis conducted on general population studies show that formulas based on CysC, alone or combined with creatinine, establish GFR as a predictor of mortality in various populations, starting from a GFR <85 mL/min/1.73 m^2 [61]. GFR values estimated with creatinine only have a J-shaped correlation with all cause of mortality. Non-GFR-related factors which influence serum creatinine levels, such as muscle mass, diet, and physical activity, alter the link between GFR and mortality [62]. Creatinine levels lower than those normally expected from the corresponding GFR values in subjects in precarious health conditions and at high risk of mortality seem to be the responsible mechanisms. Non-GFR-dependent factors which influence CysC levels seem to reinforce the association between GFR and mortality; [63] a possible explanation is that obesity, inflammation, and diabetes are all conditions that increase CysC serum levels [64]. In a recent cohort study of individuals aged 80 years or older, CKD-EPI$_{CysC}$ and CKD-EPI$_{creatinine/CysC}$ equations appear to predict with greater accuracy mortality, renal replacement therapy, and severe cardiovascular events compared with MDRD and CKD-EPI$_{creatinine}$ equations [65].

All the above-described equations have been validated and should be used in subjects aged 18–70 years old; nonetheless, CKD-EPI and MDRD should be preferred over Cockcroft–Gault formulas in elderly population [66]. MDRD and CKD-EPI equations compared to a reference GFR measurement, in older Caucasians, overestimated GFR (especially for GFR >60 mL/min/1.73 m^2), whereas CKD-EPI$_{cysC}$ was unbiased; all three CKD-EPI equations appear to be more accurate than MDRD [67]; CysC-based equations' superiority was proved not only in Caucasian elderly population [68].

At present, the latest KDIGO guidelines (2012) recommend use of CKD-EPI creatinine in clinical practice. It is suggested that CysC equations (CKD-EPI$_{CysC}$ – CKD-EPI$_{creatinine/CysC}$) be used:

- In the 59–45 mL/min/1.73 m^2 range, in the absence of markers of kidney damage for confirmation of chronic kidney disease
- In specific circumstances when GFR calculated with creatinine alone is less accurate [69]

10.2.4 BIS Equations

In 2012 the Berlin Initiative Study (BIS) research group proposed to develop new equations, accurate at estimating GFR in persons aged 70 years or more [70]. The population consisted of 610 subjects, a subset of a larger cohort study. Four variables were considered: age, sex, serum creatinine, and serum CysC. Ethnicity was not included because of the homogeneity of the population. The difference between BIS-1 and BIS-2 is the use, in the latter, of CysC. In the validation, iohexol was used as the reference test. The average age of the sample was 78.5 years old. Results were compared to the GFR estimations achieved through the known equations. Both the two new equations have shown more precision and accuracy in GFR measurement compared to the other formulas, especially in the group with values >30 mL/min/1.73 m^2. In the sample, all the other equations tended to overestimate GFR values, especially MDRD, and to a lesser extent Cockcroft–Gault. The addition of CysC values to the equation appears advantageous in the studied population, as it appears to reduce the effects of sex and age, supporting its potential use in the presence of a reduced muscle mass. Both equations confirm a high prevalence of GFR values <60 mL/min/1.73 m^2 in the over 70 population and the lowest rate of reclassification compared to the other formulas. The study sample consisted only of Caucasian individuals, with a slightly or moderately reduced renal function: therefore their predictive value for different ethnicities or in the case of severe renal failure is unknown. Nowadays few external validation studies exist with opposing results on the benefit of BIS compared to CKD-EPI equations in elderly [71–75]. Further validation studies of these equations in the elderly population are warranted also as a predictor of important outcomes.

Tables 10.1 and 10.2 illustrate the pros and cons of each formula, in different clinical settings [42].

In conclusion, estimation of GFR, considered easy and intuitive by most physicians, remains a complex process, especially in the elderly, and a greater awareness about the limits of the various GFR estimation formulas is auspicable.

Table 10.1 Pros and cons for each GFR-estimating formula

Equations for GFR estimation	Variables	Pros	Cons
Cockcroft–Gault – 1976	Cr Age Weight Sex	No 24-h urine collection required Easiness Widely studied	Body weight requested It correlates with ClCr, but not with GFR (GFR overestimated) Correction for body surface area is needed, in order to normalize to mL/min/1.73 m^2 Underestimation in advanced age Overestimation in the presence of overweight/obesity or edema
Four-variable MDRD – 2006	Cr Age Sex Ethnicity	Recommended by the 2002 KDOQI guidelines Widely studied Correlation to GFR Body weight not required Results already normalized for body surface area	Systematic underestimation for GFR >60 mL/min/1.73 m^2 Poorly validated in the elderly
CKD-EPI – 2009	Cr Age Sex Ethnicity	Recommended by the 2012 KDIGO guidelines Better correlation with GFR than MDRD, especially for GFR >60 mL/min/1.73 m^2	Bias due to the use of three databases Poorly validated in the elderly
CKD-EPI Cys/Cr-CysC – 2012	Cr CysC Age Sex Ethnicity	CysC less influenced by age, sex, ethnicity More accurate and precise, in particular for GFR >60 mL/min/1.73 m^2 and for BMI <20 kg/m^2 Suggested by the 2012 KDIGO guidelines in special conditions Probably more useful in case of reduced muscle mass	CysC influenced by systemic infections, thyroid dysfunction, steroidal therapies Problems for the dosage method standardization, lack of normal values range, cost Poorly validated in the elderly
BIS 1 – 2012	Cr Age Sex	More precision and better correlation with mGFR in the elderly, especially with GFR >30 mL/min/1.73 m^2	Validated for Caucasians only Validated for over 70 years old subjects only Limited external validation
BIS 2 – 2012	Cr CysC Age Sex	More precision and better correlation with mGFR in the elderly, especially with GFR >30 mL/min/1.73 m^2 CysC less influenced by age, sex, ethnicity Probably more useful in case of reduced muscle mass	

Table 10.2 GFR-estimating formulas in different clinical context

Subgroup	Suggested equation	To avoid/not suggested equation
Age included between 18 and 70 years old	MDRD; CKD-EPI$_{Cr}$; CKD-EPI$_{CysC}$; CKD-EPI$_{Cr\text{-}CysC}$	BIS-1 and BIS-2
Age >70 years old	CKD-EPI$_{Cr}$; CKD-EPI$_{CysC}$; CKD-EPI$_{Cr\text{-}CysC}$; BIS-1 and BIS-2[a]	C-G
Normal weight	MDRD; CKD-EPI$_{Cr}$; CKD-EPI$_{CysC}$; CKD-EPI$_{Cr\text{-}CysC}$; BIS-1, BIS-2 if old and GFR >30 mL/min/1.73 m^{2}[a]	
Overweight (BMI >25 kg/m^2) or edema	MDRD; CKD-EPI$_{Cr}$; CKD-EPI$_{CysC}$; CKD-EPI$_{Cr\text{-}CysC}$	C-G
Underweight (BMI <20 kg/m^2), sarcopenia, amputations, cachexia	C-G (?); CKD-EPI$_{Cys\ c}$; CKD-EPI$_{Cr\text{-}Cys\ c}$; BIS-2 if old and GFR >30 mL/min/1.73 m^{2}[a]	
GFR >60 mL/min/1.73 m^2	CKD-EPI$_{Cr}$;CKD-EPI$_{CysC}$;CKD-EPI$_{Cr\text{-}CysC}$	MDRD, BIS-1
GFR <60 mL/min/1.73 m^2	MDRD; CKD-EPI$_{Cr}$; CKD-EPI$_{CysC}$; CKD-EPI$_{Cr\text{-}CysC}$; BIS-1, BIS-2 if old and GFR>30 mL/min/1.73 m^{2}[a]	
Ethnicity other than Caucasian	MDRD; CKD-EPI$_{Cr}$; CKD-EPI$_{CysC}$; CKD-EPI$_{Cr\text{-}CysC}$	BIS-1 and BIS-2

[a]Validated in Caucasian only; *BIS* Berlin Initiative Study; *BIS-1* BIS formula with serum creatinine, sex, and age included; *BIS-2* BIS formula with cystatin C, serum creatinine, sex, and age included; *BMI* body mass index; *ClCr* creatinine clearance; *C-G* Cockcroft–Gault equation; *CKD-EPI* Chronic Kidney Disease Epidemiology Collaboration; *Cr* serum creatinine; *Cr-CysC* formulas based on the combined use of serum creatinine and cystatin C; *CysC* cystatin C; *GFR* glomerular filtration rate; *mGFR* measured glomerular filtration rate; *MDRD* Modification of Diet in Renal Disease

Bibliography

1. Bolignano D, Mattace-Raso F, Sijbrands EJ, Zoccali C. The aging kidney revisited: a systematic review. Ageing Res Rev. 2014;14:65–80.
2. Baylis C, Schmidt R. The aging glomerulus. Semin Nephrol. 1996;16:265–76.
3. Anderson S, Brenner BM. Effects of aging on the renal glomerulus. Am J Med. 1986;80:435–42.
4. Kappel B, Olsen S. Cortical interstitial tissue and sclerosed glomeruli in the normal human kidney, related to age and sex. A quantitative study. Virchows Arch A Pathol Anat Histol. 1980;387:271–7.
5. Brenner BM. Hemodynamically mediated glomerular injury and the progressive nature of kidney disease. Kidney Int. 1983;23:647–55.
6. Hill GS, Heudes D, Bariety J. Morphometric study of arterioles and glomeruli in the aging kidney suggests focal loss of autoregulation. Kidney Int. 2003;63:1027–36.
7. Musso CG, Oreopoulos DG. Aging and physiological changes of the kidneys including changes in glomerular filtration rate. Nephron Physiol. 2011;119:1–5.
8. Fliser D, Ritz E. Renal hemodynamics in the elderly. Nephrol Dial Transplant. 1996;11:2–8.
9. Lindeman RD, Goldman R. Anatomic and physiologic age changes in the kidney. Exp Gerontol. 1986;21:379–406.

10. Laucks Jr SP, McLachlan MS. Aging and simple cysts of the kidney. Br J Radiol. 1981;54:12–4.
11. Martin JE, Sheaff MT. Renal ageing. J Pathol. 2007;211:198–205.
12. Rowe JW, Shock NW, DeFronzo RA. The influence of age on the renal response to water deprivation in man. Nephron. 1976;17:270–8.
13. Sands JM. Urine-concentrating ability in the aging kidney. J Gerontol A Biol Sci Med Sci. 2012;67:1352–7.
14. Fliser D, Franek E, Joest M, Block S, Mutschler E, Ritz E. Renal function in the elderly: impact of hypertension and cardiac function. Kidney Int. 1997;51:1196–204.
15. Epstein M, Hollenberg NK. Age as a determinant of renal sodium conservation in normal man. J Laborat Clin Med. 1976;87:411–7.
16. Crane MG, Harris JJ. Effect of aging on renin activity and aldosterone excretion. J Laborat Clin Med. 1976;87:947–59.
17. Luft FC, Weinberger MH, Fineberg NS, Miller JZ, Grim CE. Effects of age on renal sodium homeostasis. Am J Med. 1987;82:9–15.
18. Ohashi M, Fujio N, Nawata H, Kato K, Ibayashi H, Kangawa K, Matsuo H. High plasma concentrations of human atrial natriuretic polypeptide in aged men. J Clin Endocrinol Metabol. 1987;64:81–5.
19. Perazella MA, Mahnensmith RL. Hyperkalemia in the elderly: drugs exacerbate impaired potassium homeostasis. J Gen Intern Med. 1997;12:646–56.
20. Frassetto LA, Morris Jr RC, Sebastian A. Effect of age on blood acid–base composition in adult humans: role of age-related renal functional decline. Am J Physiol. 1996;271:1114–22.
21. Yamada H, Sacktor B, Kinsella J. Age-associated changes in ammoniagenesis in isolated rat renal tubule segments. Am J Physiol. 1992;262:600–5.
22. Adler S, Lindeman RD, Yiengst MJ, Beard E, Shock NW. Effect of acute acid loading on urinary acid excretion by the aging human kidney. J Laborat Clin Med. 1968;72:278–89.
23. Agarwal BN, Cabebe FG. Renal acidification in elderly subjects. Nephron. 1980;26:291–5.
24. Luckey AE, Parsa CJ. Fluid and electrolytes in the aged. Arch Surg. 2003;138:1055–60.
25. Nakhoul FZC, Levin M, Gteen J, Winavet J, Better OS. Urinary acidification capacity in the elderly. Geriatr Nephrol Urol. 1995;5:149–55.
26. Alpern RJ. Trade-offs in the adaptation to acidosis. Kidney Int. 1995;47:1205–15.
27. Hollenberg NK, Adams DF, Solomon HS, Rashid A, Abrams HL, Merrill JP. Senescence and the renal vasculature in normal man. Circ Res. 1974;34:309–16.
28. Davidson AJ, Talner LB, Downs 3rd WM. A study of the angiographic appearance of the kidney in an aging normotensive population. Radiology. 1969;92:975–83.
29. Long DA, Mu W, Price KL, Johnson RJ. Blood vessels and the aging kidney. Nephron Exp Nephrol. 2005;101:95–9.
30. Wesson LG. Renal hemodynamics in physiological states. In: Wesson LG, editor. Physiology of the human kidney. New York: Grune & Stratton; 1969. p. 96.
31. Fliser D, Zeier M, Nowack R, Ritz E. Renal functional reserve in healthy elderly subjects. J Am Soc Nephrol. 1993;3:1371–7.
32. Hollenberg NK, Adams DF, Solomon HS, Rashid A, Abrams LA, Merill JP. Senescence and the renal vasculature in normal men. Circ Res. 1974;34:309–16.
33. Lindeman RD. Is the decline in renal function with normal aging inevitable? Geriatr Nephrol Urol. 1998;8:7–9.
34. Epstein M. Aging and the kidney. J Am Soc Nephrol. 1996;7:1106–22.
35. Casellas D, Moore LC. Autoregulation and tubuloglomerular feedback in juxtaglomerular arterioles. Am J Physiol. 1990;258:F660–9.
36. Johnson PC. Autoregulation of blood flow. Circ Res. 1986;59:483–95.
37. Lorenz JN, Weihprecht H, Schnermann J, Skitt O, Briggs JP. Renin release from isolated juxtaglomerular apparatus depends on macula densa chloride transport. Am J Physiol. 1991;260:F486–93.
38. Arendshorst WJ, Brannstrom K, Ruan X. Actions of angiotensin II on renal microvasculature. J Am Soc Nephrol. 1999;10:S149–61.

39. Kurokawa K. Tubuloglomerular feedback: its physiological and pathophysiological significance. Kidney Int. 1998;54:S71–4.
40. Schnermann J, Briggs JP. Restoration of tubuloglomerular feedback in volume-expanded rats by angiotensin II. Am J Physiol. 1990;259:F565–72.
41. Kenney WL, Zappe DH. Effect of age on renal blood flow during exercise. Aging Clin Exp Res. 1994;6:293–302.
42. Castellani S, Ungar A, Cantini C, La Cava G, Di Serio C, Altobelli A, Vallotti B, Pellegri M, Brocchi A, Camaiti A, Coppo M, Meldolesi U, Messeri G, Masotti G. Excessive vasoconstriction after stress by the aging kidney: inadequate prostaglandin modulation of increased endothelin activity. J Lab Clin Med. 1998;132:186–94.
43. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16:31–41.
44. Cirillo M, Anastasio P, De Santo NG. Relationship of gender, age, and body mass index to errors in predicted kidney function. Nephrol Dial Transplant. 2005;20:1791–8.
45. Winter MA, Guhr KN, Berg GM. Impact of various body weights and serum creatinine concentrations on the bias and accuracy of the Cockcroft-Gaul equation. Pharmacotherapy. 2012;32:604–12.
46. Levey AS, Bosch JP, Lewis JB. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Ann Intern Med. 1999;130:461–70.
47. Levey AS, Coresh J, Greene T. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Ann Intern Med. 2006;145:247–54.
48. Stevens LA, Coresh J, Feldman HI. Evaluation of the modification of diet in renal disease study equation in a large diverse population. J Am Soc Nephrol. 2007;18:2749–57.
49. Poggio ED, Wang X, Greene T. Performance of the modification of diet in renal disease and Cockcroft-Gault equations in the estimation of GFR in health and in chronic kidney disease. J Am Soc Nephrol. 2005;16:459–66.
50. Gaspari F, Ferrari S, Stucchi N. Performance of different prediction equations for estimating renal function in kidney transplantation. Am J Transplant. 2004;4:1826–35.
51. Ibrahim H, Mondress M, Tello A. An alternative formula to the Cockcroft-Gault and the modification of diet in renal diseases formulas in predicting GFR in individuals with type 1 diabetes. J Am Soc Nephrol. 2005;16:1051–60.
52. Ma Y-C, Zuo L, Chen J-H. Modified Glomerular Filtration Rate estimating equation for Chinese patients with chronic kidney disease. J Am Soc Nephrol. 2006;17:2937–44.
53. Matsuo S, Imai E, Horio M. Revised equations for estimated GFR from serum creatinine in Japan. Am J Kidney Dis. 2009;53:982–92.
54. Levey AS, Stevens LA, CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150:604–13.
55. Matsushita K, Mahmoodi BK, Chronic Kidney Disease Prognosis Consortium. Comparison of risk prediction using the CKD-EPI equation and the MDRD study equation for estimated glomerular filtration rate. JAMA. 2012;307:1941–51.
56. Randers E, Kornerup K, Erlandsen EJ. Cystatin C levels in sera of patients with acute infection diseases with high C-reactive protein levels. Scand J Clin Lab Invest. 2001;61:333–5.
57. Fricker M, Wiesli P, Brändle M. Impact of thyroid dysfunction on serum cystatin C. Kidney Int. 2003;63:1944–7.
58. Risch L, Herklotz R, Blumberg A. Effects of glucocorticoid immunosuppression on serum cystatin C concentrations in renal transplant patients. Clin Chem. 2001;47:2055–9.
59. Kottgen A, Selvin E, Stevens LA. Serum cystatin C in the United States: the Third National Health and Nutrition Examination Survey (NHANES III). Am J Kidney Dis. 2008;51:385–94.
60. Inker LA, Schmid CH, CKD- EPI Investigators. Estimating glomerular filtration rate from serum creatinine and cystatin C. N Engl J Med. 2012;367:20–9.

61. Shlipak MG, Matsushita K, CKD Prognosis Consortium. Cystatin C versus creatinine in determining risk based on kidney function. N Engl J Med. 2013;369:932–43.
62. Oterdoom LH, Gansevoort RT, Schouten JP. Urinary creatinine excretion, an indirect measure of muscle mass, is an independent predictor of cardiovascular disease and mortality in the general population. Atherosclerosis. 2009;207:534–40.
63. White SL, Polkinghorne KR, Atkins RC. Comparison of the prevalence and mortality risk of CKD in Australia using the CKD Epidemiology Collaboration (CKD-EPI) and Modification of Diet in Renal Disease (MDRD) Study GFR estimating equations: the AusDiab (Australian Diabetes, Obesity and Lifestyle) Study. Am J Kidney Dis. 2010;55:660–70.
64. Mathisen UD, Melsom T, Ingebretsen OC. Estimated GFR associates with cardiovascular risk factors independently of measured GFR. J Am Soc Nephrol. 2011;22:927–37.
65. Van Pottelbergh G, Vaes B, Adriaensen W. The glomerular filtration rate estimated by new and old equations as a predictor of important outcomes in elderly patients. BMC Med. 2014;12:27.
66. Flamant M, Haymann JP, Vidal-Petiot E. GFR estimation using the Cockcroft-Gault, MDRD study, and CKD-EPI equations in the elderly. Am J Kidney Dis. 2012;60:847–9.
67. Kilbride HS, Stevens PE, Eaglestone G. Accuracy of the MDRD (Modification of Diet in Renal Disease) study and CKD-EPI (CKD Epidemiology Collaboration) equations for estimation of GFR in the elderly. Am J Kidney Dis. 2013;61:57–66.
68. Pei X, Bao L, Xu Z. Diagnostic value of cystatin C and glomerular filtration rate formulae in Chinese nonelderly and elderly populations. J Nephrol. 2013;26:476–84.
69. KDIGO. Clinical practice guidelines for the evaluation and management of chronic kidney disease. Kidney Int Suppl. 2013;3:1–150.
70. Schaeffner ES, Ebert N, Delanaye P. Two novel equations to estimate kidney function in persons aged 70 years or older. Ann Intern Med. 2012;157:471–81.
71. Koppe L, Klich A, Dubourg L. Performance of creatinine-based equations compared in older patients. J Nephrol. 2013;26:716–23.
72. Vidal-Petiot E, Haymann JP, Letavernier E. External validation of the BIS (Berlin Initiative Study)-1 GFR estimating equation in the elderly. Am J Kidney Dis. 2014;63:865–7.
73. Alshaer IM, Kilbride HS, Stevens PE, Eaglestone G, Knight S, Carter JL, Delaney MP, Farmer CK, Irving J, O'Riordan SE, Dalton RN, Lamb EJ. External validation of the Berlin equations for estimation of GFR in the elderly. Am J Kidney Dis. 2014;63:862–5.
74. Lopes MB, Araújo LQ, Passos MT. Estimation of glomerular filtration rate from serum creatinine and cystatin C in octogenarians and nonagenarians. BMC Nephrol. 2013;14:265.
75. Liu X, Chen J, Wang C. Assessment of glomerular filtration rate in elderly patients with chronic kidney disease. Int Urol Nephrol. 2013;45:1475–82.