Nephrogeriatrics: Evaluation of Renal Function in the Elderly Today

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Introduction

Due to the transition of the population pyramid worldwide, the elderly population increases every time. As a result, prevalence of chronic diseases also increases. One of them is chronic kidney disease (CKD) which is a pathology considered a public health problem that can trigger in kidney failure, dialysis [1], cardiovascular disease [2], cognitive impairment [3], dementia [3] and early death [4].

Most patients diagnosed with CKD are over 65, elderly population. To evaluate the renal function in the elderly, the importance is not what method to use. It is essential to know aspects such as inherent changes in the kidney aging process and the chronically diminished glomerular filtration rate. Then, the physiological glomerular filtration rate will be the protagonist. Also, other formulas that exclude creatinine will be very useful to calculate the glomerular filtration rate in the elderly.

This would avoid over diagnosis of chronic kidney disease in the geriatric population, which already has other comorbidities that can hide the loss of renal function, and therefore the consequences of expensive and unnecessary treatments. This mini review investigates the benefit of the equations that estimate GFR and biomarkers of renal function in the elderly population. This theme is very important to everyday praxis.

The difficulty of establishing the glomerular filtration rate in the elderly

The KDOQI guidelines define chronic kidney disease (CKD) as a decrease in GFR <60 ml/min/1.73m^2 for more than three months [5]. But this definition could be doubtful in the elderly if we consider that during the aging process there are a series of changes in renal structure and function. This clearly causes a net physiological decrease in renal functional reserve [6].

Renal aging is associated with progressive functional decrease, thickening of the glomerular basement membrane, mesangial expansion and focal glomerulosclerosis. The kidney presents a gradual decrease in weight that begins between 40 to 50 years of

approximately 10% per decade. The decrease in GFR decreases by 1% per year after the age of 30, it is estimated that at 80 years, 60% will have decreased renal function by approximately 40-50%. On average 0.87 to 1.05 ml/minute/year is lost [7]. In the Framingham Offspring study, it was shown that for each decade the odds ratio for developing CKD was 2.56 [8].

In addition, there are other confounding factors that can accelerate the reduction of GFR such as: atherosclerosis, hypertension, left ventricular dysfunction, glucoseintolerance, diabetes mellitus, obesity, heart failure, smoking, disabling diseases, fragility, protein intake in the diet [9,10].

Traditional formulas such as The Cockcroft-Gault (CG) with sensitivity (78%) and specificity (94%), the Modification of Diet in Renal Disease (MDRD) with sensitivity (70%) and specificity (94%) and the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) with sensitivity (50,5%) and specificity (85%) use the glomerular filtration rate (GFR) to diagnose CKD. The most commonly used biomarker for estimating GFR is creatinine. It is inaccurate in the elderly due to the loss of muscle mass, malnutrition, dehydration and frailty [11]. Estimation of creatinine clearance is essential; however, a 24-hour urine collection for creatinine clearance may be skewed in elderly patients due to inaccurate or incomplete urine collection [12].

The recently developed Lund Malmö equation (LMREV cr.) was more accurate across subgroups than MDRD and CKD-EPI. There is evidence suggesting that both MDRD and CKD-EPI may overestimate GFR not only among elderly but also among young adults. In configurations similar to the LCS cohort, LM Revised should prefer MDRD and CKD-EPI in the estimation of the GFR due to its superior precision and its more stable performance in GFR, age and BMI intervals regardless of gender. Although, the generalization of the findings in clinical settings to geriatric patients and hospitalized patients is uncertain [13].

Regarding the CKD EPI formula that combines cystatin C and creatinine (CKD-EPI cr-cys), it was significantly more accurate than all creatinine based equations except LMREVcrin an elderly

population and the accuracy was low when the eGFR was <45 mL/min/1.73m. Thus, this formula can be used in vulnerable elderly and with poly pharmacy, but more studies are needed [14].

Proteinuria defined as the persistent excretion of protein in urine equal to or greater than 150 mg per day is a determining factor in the decrease of the GFR [15]. The best estimate of proteinuria is made with 24-hour urine collection and total protein or albumin levels that must be corrected for creatinine in the urine. But, these tests are difficult and time consuming. In contrast, the dipstick is a cheap, fast and available diagnostic tool [16].

However, there are some false positives such as extenuating effort, infectious processes with fever, stress [14] and sarcopenia [16]. Some studies suggest that there may be an association between sarcopenia, decreased renal function and chronic kidney disease. CKD can produce sarcopenia, and viceversa [17]. Further, urinalysis with emphasis on the severity proteinuria (5 grades ranging from negative to ≥ 3), should be included in the evaluation of the kidney function in the elderly, particularly in initial stages of CKD (i.e., stage 3a) [18].

Another parameter that is used to establish CKD is the albumin to creatinine ratio (UACR) with sensitivity (43.6%) and specificity (93%) [19]. It is a tool which measures the exact concentration of albumin in the urine and divides it by the concentration of creatinine in that same urine. The Albumin/creatinine ratio (ACR) ≥ 30mg/g (≥ 3 mg/mmol), is used as a marker of renal damage and is used to define chronic kidney disease along with low GFR. The advantages are: It can be used to detect very low levels of albumin excretion. It is not confounded by urinary concentration or dilution and it can be used to estimate one's 24-hour albumin excretion [20]. The detection of low levels of albumin excretion (micro albuminuria) has been linked to the identification of incipient diabetic kidney disease [21].

The serum concentration of cystatin C with sensitivity (61,22%) and specificity (60,34%) is a good marker of renal dysfunction (i.e., reduced GFR) than the plasma concentration of creatinine in elderly patients with plasma creatinine concentrations within the normal range [22]. Thus, this endogenous marker would be more accurate, correlates better with renal function and has the potential advantage of improving the accuracy of the clinical trial. The disadvantages include its high cost and low availability in laboratories [23].

The (99m) Tc-diethylenetriaminepentaacetic acid ((99m) Tc-DTPA) is an isotope that has been used to improve the evaluation of GFR. In a study conducted by Maioli, et al. concluded that in elderly patients, the formulas based on serum creatinine CKD-EPI and MDRD to estimate GFR can overestimate this compared to the measure with (99m) Tc- DTPA [24].

A systematic review was posed on this research question: What is the best method that could be applied in clinical practice to assess renal function in the elderly? He compared studies that used inulin, Cr-51-EDTA, Tc-DTPA or iohexol assays as the gold standard for evaluating kidney function and concluded that there is no precise method to evaluate kidney function in the elderly. The serum concentration of cystatin C and the MDRD formulas could be valuable parameters, although there is still insufficient evidence to corroborate this information [25].

In those clinical situations in which we have a reduced GFR, particularly in the aging population, where it can be complicated to establish whether this reduction is due to a physiological aging process or due to a renal pathological process, the HUGE formula could be of great help as screening of CKD. In 2011, a new HUGE (Hematocrit, urea, gender) equation emerges in Spain with the study by Alvarez-Gre-gori, et al. which can detect CKD without using the patient's GFR. This formula offers a detection of CKD only based on the patient's gender, hematocrit, and blood urea levels [26].

However, elderly patients are often associated with various co-morbidities, which may cause fluctuations in the levels of these two parameters. Unfortunately we could not avoid these confounding effects when we apply the equation. So it is important to clarify that the HUGE formula is not to make a diagnosis. Apparently, the HUGE equation with a score greater than or equal to zero is more accurate than other equations for estimating GFR (MDRD, CKD-EPI). The formula was validated in some countries such as Argentina and Spain with a sensitivity (92,80%) and specificity (96,05%), positive predictive value (92,94%) and negative predictive value (93,89%) [27,28]. In a follow-up study of elderly patients for 8 years, none had a base line value of HUGE >0, while all patients with HUGE >0 died at follow-up.

This finding would emphasize the usefulness of this equation, not only as a screening to identify elderly patients with renal disease, but also to patients at high mortality risk. The HUGE formula has demonstrated the ability to discern, in those patients with diabetic nephropathy, those who have more risk of progressive renal failure [6]. This formula has also been associated with long-term vital prognosis in non-hospitalized elderly and cardiovascular risk [29].

Therefore it is useful to differentiate CKD in those individuals with low GFR who could only be physiological or attributed to aging. To determine if GFR is physiological, the Keller equation is used, which

Table 1: Equations GFR.

Keller	Estimated creatinine clearance (ml/min): (130-edad [en años] ml/min)
Cockcroft–Gault	Estimated creatinine clearance (ml/min): [(140-age) weight]/[72 × serum creatinine (mg/dl)] (0.85 if woman)
MDRD	Estimated glomerular filtration rate (ml/min/1.73m²): (186 [serum creatinine (mg/dl)] 1.154 [age (years)] 0.203 [0.742 if woman] [1.21 if African-American]) to give result in ml/min body surface area/1.73
CKD-EPI	Estimated glomerular filtration rate (ml min⁻¹ 1.73 m⁻²) if serum creatinine concentrations are >0.9 mg dl⁻¹ (male) and >0.7 mg dl⁻¹ (female): men, $141 \times [Scr \text{ (in mg dl}^{-1})/0.9]^{-0.411} \times (0.993)^{Age}$; and women, $144 \times [Scr \text{ (in mg dl}^{-1})/0.7]^{-0.329} \times (0.993)^{Age}$
LM Revised	Estimated glomerular filtration rate by Revised Lund-Malmö Study equation: $eX-0.0158 \times Age+0.438 \times \ln (Age)$ Femalep Cr < 150 mmol/L: $X = 2.50+0.0121 \times (150-pCr)$ Femalep Cr ≥ 150 mmol/L: $X = 2.50-0.926 \times \ln (pCr/150)$ Malep Cr < 180 mmol/L: $X = 2.56+0.00968 \times (180-pCr)$ Malep Cr ≥ 180 mmol/L: $X = 2.56-0.926 \times \ln (pCr/180)$
HUGE	Estimated glomerular filtration rate=$2.505458-[0.264418 \times hematocrit]+[0.118100 \times serum \text{ urea (mg/dl)}]+[1.383960 \text{ if male}]$

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will guide the physician to an approximate age-normal GFR value and avoid over diagnosing CKD (Table 1).

Summary of the evidence

Not all the elderly with decreased GFR have CKD [30]. The misdiagnosis of CKD can create anguish and worry in the patient and their relatives, also generates more expenses for the health system [26]. This is why it is important to know and apply in daily clinical practice the use of the physiological glomerular filtration rate when applying the equation of Keller [21-33] and HUGE in elderly over 70 years to establish a possible CKD in this group population. More studies are needed that include the aging population to replicate equations that are useful in daily clinical practice.

Conclusions

The loss of GFR associated with age depends on the aging process of the renal system itself, as well as other associated comorbidities, such as diabetes, hypertension, heart failure, and frailty.

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