REVIEW ARTICLE

Port J Nephrol Hypert 2014; 28(1): 22-30
Advance Access publication 14 March 2014

Equations for glomerular filtration rate estimation use in the elderly

Utilização de equações para estimar o débito do filtrado glomerular nos idosos

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Received for publication: 26/02/2014
Accepted: 03/03/2014

ABSTRACT

Chronic kidney disease (CKD) has been increasingly diagnosed in the elderly, though its clinical significance is still matter of debate. Serum creatinine and cystatin C are the most used endogenous renal function markers. Several equations, usually adjusted for demographical variables, have been derived from them, in order to estimate glomerular filtration rate. Serum creatinine levels are influenced by muscle mass so, in patients frequently sarcopenic as the elderly, tends to overestimate renal function. Differently, serum cystatin C seems to improve kidney function estimation in the elderly, although the best performance results have been obtained with equations that include both markers. Creatinine is more widely used than cystatin C, with MDRD and EPI being the most common creatinine-based equations. The EPI equation has been shown to improve significantly GFR estimation in subjects with no or mild kidney dysfunction, without jeopardizing eGFR performance in subjects with advanced CKD. Moreover, epidemiological studies have shown that EPI equation may allow a more clinically relevant identification of chronic kidney disease patients. Nevertheless, in the elderly population, one should not overemphasize the issue of GFR accurate estimation, but rather appreciate the probability of kidney dysfunction progression, taking into account the competitive risk between end-stage renal disease and death. Several studies have demonstrated that cystatin C-based (with or without creatinine) equations have considerable better prediction ability than creatinine-only based equations, particularly for death and cardiovascular events. Considering end-stage renal disease, results are more conflicting, although a recent meta-analysis has shown that in the elderly population cystatin C-based equations presented the best predictive behaviour. Thus, we stress the need for an individualized use of glomerular filtration rate equations in the elderly, in whom they should be regarded less as accurate estimators, but more as predictors of clinical outcomes, allowing for their use to be more judicious and clinically relevant.

Key-words: Clinical outcomes; creatinine; cystatin C; renal function.

RESUMO

O diagnóstico de doença renal crónica tem aumentado na população idosa, embora o seu significado clínico seja ainda debatido. A creatinina sérica e cistatina C são os marcadores endógenos de função renal mais utilizados. Várias equações, ajustadas para variáveis demográficas, foram derivadas destes marcadores com o objectivo de estimar o débito do filtrado glomerular. O valor de creatinina sérica é influenciado pela massa muscular pelo que, nos indivíduos com redução da massa muscular como é o caso dos idosos, tende a sobrestimar a função renal. Por outro lado, a cistatina C parece melhorar a estimativa da função renal nos idosos, embora o melhor desempenho tenha sido observado com as equações que incluem ambos os marcadores. A creatinina é mais utilizada do que a cistatina C, sendo as equações MDRD e EPI derivadas da creatinina, as mais usadas. Foi demonstrado que a equação EPI melhora significativamente a estimativa do débito de filtrado glomerular na população sem ou com ligeira disfunção renal, sem comprometer o desempenho em indivíduos com doença renal crónica avançada. Mais ainda, estudos epidemiológicos mostraram que a utilização da equação EPI permitirá uma identificação mais relevante dos doentes com doença renal crónica. Contudo, na população idosa não devemos enfatizar demasiado a necessidade de uma estimativa exata da filtração glomerular, mas sim avaliar a probabilidade de progressão da disfunção renal, tendo em conta o risco competitivo entre doença renal crónica terminal e morte. Vários estudos demonstraram que as equações derivadas da cistatina C (com ou sem creatinina), têm uma melhor capacidade preditiva, relativamente às equações derivadas unicamente da creatinina, no que se refere aos eventos cardiovasculares e à mortalidade. Relativamente à doença renal crónica terminal os resultados são mais controversos, embora uma metanálise recente mostrou que na população idosa as equações derivadas da cistatina C apresentam o melhor valor preditivo. Assim, sublinhamos a necessidade de uma utilização individualizada destas equações na população idosa, na qual estas devem ser valorizadas não tanto como estimadores precisos de função, mas mais como preditores de eventos clínicos, permitindo que a sua utilização seja mais criteriosa e clinicamente relevante.

Palavras-chave: Cistatina C, creatinina, eventos clínicos, função renal.

INTRODUCTION

Chronic kidney disease (CKD) has increasingly been considered a public health problem and a research priority[1] and is associated with an increased risk for all cause and cardiovascular mortality[2].

It is predominantly a disease of the elderly, who are the fastest growing end-stage renal disease (ESRD) group in USA and Europe[3,4], including Portugal, where patients over 65 years correspond to 57.6% of total ESRD incident population (Data from SPN registry 2012).

An accurate assessment of kidney function has several clinical implications, such as timely referral to nephrology, adequate drug dose adjustment, improved decision making in imaging testing and adequate renal replacement therapy consideration. Furthermore, an early detection and treatment of CKD may prevent or delay progression to ESRD.

The glomerular filtration rate (GFR) is considered to be the best indicator of kidney function, but methods to measure GFR using exogenous markers, such as inulin clearance, Cr-EDTA or Tc-DTPA, are laborious as well as expensive, being rarely used in clinical practice. Therefore, endogenous markers, such as serum creatinine or cystatin C, are used to estimate kidney function. Equations using these markers adjusted to other variables (mainly demographical) are an attempt to improve accuracy in estimation of GFR (eGFR). However, none of these eGFR equations have been validated in a large population of elderly patients.

In this article, we aim to review the performance and limitations of these endogenous markers and

their equations as estimators of GFR in the elderly. Additionally, the ability of the different eGFR equations in predicting significant clinical outcomes (ESRD, death) will be sought.

ENDOGENOUS MARKERS

Serum Creatinine

Serum creatinine (SCr), as a marker of renal function, continues to be widely used, in spite of inaccuracies in its measurement and interferences in its turnover, tubular secretion and production rate, which is mainly dependent of the muscle mass[5].

Renal function deteriorates by 8 ml/min per decade in the ageing population, although there is a wide intra-individual variability[6]. The loss of renal parenchyma with ageing accounts for this change, but decreased muscle mass seen in the elderly, resulting in a decrease of creatinine production, also influences renal function measurement[7].

Lower SCr levels have been reported in subjects with vitamin D deficiency, which has a high prevalence in the elderly, and probably increases the rate of loss of muscle mass in this population along with a decrease in muscle strength[8].

In addition, SCr measurement by the most common method (Jaffé) is subject to interferences by chromogens, such as bilirubin, glucose and uric acid. Similarly, the enzymatic method is prone to interference by bilirubin and some antibiotics. Large variations between laboratories in calibration of the SCr assays may also lead to inaccuracies in its determination[9]. Recently, an attempt to standardize measurement has been introduced by adoption of a common calibration to isotope dilution mass spectrophotometry standard with substantial improvement and traceability of SCr measurements[10].

Some authors reported several limitations with SCr as a GFR marker in older patients. Swedko *et al.*[11] reported that an SCr level greater than 1.7 mg/dL had almost perfect specificity but only 12.6% sensitivity for the detection of CKD (GFR ≤ 50 mL/min), in patients 65 years or older. This inability to diagnose CKD in older patients based only in SCr was also found by others[12]. Branten *et al.*[13] reported that hypoalbuminaemia influences the tubular SCr secretion leading to errors in estimation of GFR, highlighting the limitations of SCr as a kidney function marker in patients with nephrotic syndrome.

Creatinine Clearance

Creatinine Clearance (CCr), as measured from 24-h urine collection, is often used in clinical practice to measure GFR, but it overestimates GFR due to creatinine secretion by the renal tubules and the inherent limitations of SCr as a kidney marker. Moreover, CCr is susceptible to urine collection errors, especially in elderly patients[14], thus being a poor screening test for CKD.

Serum Cystatin C

Cystatin C is a 122–amino acid, 13-kDa protein that is a member of a family of competitive inhibitors of lysosomal cysteine proteinases. Its functions include involvement in extracellular proteolysis, immune modulation, and antibacterial and antiviral activities.

Cystatin C has several properties that make it a good candidate as a kidney function marker, including a constant production rate regulated by a gene expressed in all nucleated cells, free filtration at the glomerulus, complete reabsorption and catabolism by the proximal tubules with no reabsorption into the bloodstream, and no renal tubular secretion[15].

Most studies have shown that serum cystatin C levels correlate better with GFR than does SCr alone, especially at higher levels of GFR, and it was also thought to be less influenced by certain demographic factors such as age, race, gender, or muscle mass compared with SCr[16,17]. But, emerging new data have shown that it is, in fact, influenced by some of these factors.

Knight *et al.*[18], in a cross-sectional study, found that older age, male gender, greater weight, greater height, current cigarette smoking, and higher serum C-reactive protein (CRP) levels were independently associated with higher serum cystatin C levels after adjusting for CCr.

A recent study, although not focusing solely on elderly people, concluded that cystatin C was 9% lower in women and 6% higher in blacks for a given GFR[19]. Similarly, another recent study that reported population distributions of cystatin C in the United States using sera samples from the Third National Health and Nutritional Examination Survey noted that abnormal cystatin C was more prevalent with increasing age[20]. Moreover, in certain clinical settings, cystatin C level may be biased as a marker of kidney function, such as in patients with rapid cell turnover, uncontrolled thyroid disease and those under steroid therapy[21].

GFR ESTIMATION FROM SERUM CREATININE BASED EQUATIONS

Cockcroft-Gault (CG) equation

Cockcroft-Gault formula (CG) is one of the most widely used equations to estimate endogenous CCr, even among elderly people, although it was originally derived from mostly younger subjects, with only 24% older than 70 years and 4% female representation[22].

This equation provides an estimate of CCr, which is not equivalent to eGFR due to the effect of creatinine tubular secretion. Moreover, this equation is not adjusted for body surface area, using instead body weight as a surrogate for muscle mass, so it overestimates CCr in oedematous states and in obese patients[23], with bad performance in subjects with extreme weight.

Studies indicate that it actually underestimates GFR in the elderly, especially at higher GFR values. Verhave *et al.*[24] reported that the CG equation underestimates GFR in patients over 65 years old. In addition, Cirrilo *et al.*[25] have found that the CG equation systematically underestimated GFR in the elderly. Nevertheless, most of the estimated values using this equation were within 30% of measured GFR, which is an acceptable performance and superior to SCr alone.

Modification of Diet in Renal Disease (MDRD) Equation

The MDRD study equation[26] was developed using data from 1628 middle-aged patients with a GFR below 60 ml/min, none diabetic, for the estimation of GFR adjusted for 1.73m$^{2\cdot}$ This equation was re-expressed[27] with SCr standardized to the reference methods using isotope dilution mass spectrometry (IDMS). The MDRD equation has been recommended by the KDOQI Study Group for CKD diagnosis and classification[28]. It has several advantages over the CG equation including providing an estimate of GFR rather than CCr.

However, the MDRD equation also has several limitations, namely being less accurate at eGFR levels above 60 ml/min per 1.73 m^2. Consequently, it may lead to misdiagnosis and misclassification of CKD in individuals with mild CKD[29]. Another limitation is the existence of differences between various laboratories regarding the calibration of the SCr assay that leads to differences in GFR estimation[30]. The effect of the calibration of SCr assay was also reported in older patients[31] with the CG formula underestimating eGFR, whereas the MDRD Study equation overestimated it.

Notwithstanding, MDRD equation has been considered as more accurate for the elderly in comparison with the CG formula[32], and is especially advantageous for elderly people compared with the CG formula or CCr, because it only requires serum creatinine, age, gender and race, but not weight or any urine collections. The most widely used form of MDRD in elderly people is the four-variable equation[33].

Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation

The CKD-EPI equation[34] was developed using data from 16 studies, in an attempt to create a more accurate equation than the one proposed by the MDRD Study. The MDRD Study equation was developed in a study population with CKD and a mean GFR of 40 mL/min per 1.73 m^2, whereas the CKD-EPI equation was developed in a more diverse study population, including participants with and without CKD, with a mean GFR of 68 mL/min per 1.73 m^2.

The estimated prevalence of CKD in the US by using the CKD-EPI equation was 1.6% lower than that obtained by the MDRD equation (11.5% compared to 13.1%)[35], with CKD-EPI equation having

lower bias, especially at eGFR ≥ 60 ml/min/ 1.73m2[34]. Other studies have also reported that the MDRD equation use increased the prevalence of CKD in the general population compared with the CKD-EPI formula[36], and that CKD-EPI equation improved performance in healthier populations, whereas the CKD-MDRD formula provided more reliable results regarding CKD patients[37]. A recent systematic review[38] reported that neither the CKD-EPI nor the MDRD Study equation were optimal for all populations and GFR ranges.

In the development of CKD-EPI equation[34] there were a limited number of participants older than 70 years and also incomplete data on measures of muscle mass and other conditions or medications that may influence SCr. It is important to note that even using CKD-EPI equation, the prevalence of CKD in the elderly remained high. In a meta-analysis of data from 1.1 million adults[39], CKD-EPI equation classified fewer individuals as having CKD and was a better predictor of mortality and ESRD risk than MDRD equation.

However, in a prospective population-based cohort study from France[40], the CKD-EPI and the MDRD equations provided very similar CKD prevalence and long-term risk assessment in the elderly (› 65 years). Recently, in a prospective study[41] the accuracy of these equations was tested in European subjects, 74 years or older, comparing with measured GFR by a reference method. The authors concluded that the CKD-EPI equation appeared less biased and was more accurate than the MDRD Study equation.

GFR ESTIMATION FROM SERUM CYSTATIN C–BASED EQUATIONS WITH OR WITHOUT SERUM CREATININE

Over the last decade, several serum cystatin C-based equations have been developed and proposed to estimate the GFR from serum cystatin C concentration as an alternative filtration marker[42,43] to SCr-based equations.

Overall, serum cystatin appears to be less susceptible to metabolic and extrarenal factors than SCr, namely in the elderly[44]. Therefore, serum cystatin C-based equations seem to be promising for renal function estimation in the elderly. Several studies have confirmed cystatin C as a better estimator of kidney function in the older[45,46] and in the very old[47] subjects.

Stevens et al.[19], reported an equation (CKD-EPI SCr and cystatin formula) incorporating both cystatin C and SCr in addition to age, sex, and race. This study, involving a pooled analysis of individuals with CKD, concluded that this equation provided a better estimation of GFR. In recent years, several studies analyzed the accuracy of this formula in the elderly, without unequivocal results. Bevc *et al.*[48], in a group of 317 Caucasian patients aged › 65 years, compared different equations against 51Cr-EDTA clearance, and found that a higher diagnostic accuracy was achieved with the equation that uses both SCr and cystatin C than with MDRD (P ‹ 0.013) or CKD-EPI creatinine formula (P ‹ 0.01). Interestingly, the simple cystatin C formula (100/serum cystatin C) presented similar results to the double markers formula, chiefly in patients with mild kidney dysfunction.

In a cross-sectional study[49] designed to evaluate GFR estimating equations in comparison to a measured GFR, investigators from the Berlin Initiative Study (BIS) measured GFR by iohexol clearance in a subset of 610 participants with mean age of 78.5 years. A major finding of this study was that cystatin C had a much stronger association with GFR than SCr. The addition of age and gender greatly improved SCr-based GFR estimation, but the same variables added little value to cystatin C-based eGFR. In this elderly cohort, the best GFR estimation was derived from a combined SCr and cystatin C equation; however, cystatin C-only equation was clearly superior to a creatinine-only equation.

PROGRESSION TRAJECTORY OF GFR IN ELDERLY PATIENTS WITH CHRONIC KIDNEY DISEASE

Prevalence of CKD in the elderly is, independently from the formula used, high. Published rates vary from 25%[50] to 55%[51] for stage 3-4 CKD using the MDRD formula. Yet, as important as CKD detection, is the understanding of how CKD progresses in the aged population, because it would enable a more

targeted provision of care, particularly for ESRD-related assessments.

The rate of loss of kidney function has been estimated around 7-8 ml/min/decade in subjects over the age of 30[52]. Few studies have addressed this issue specifically in the elderly. In a Canadian cohort of about 10 000 subjects over 65 years, with an eGFR (by MDRD equation) at baseline < 90 ml/min, the age-adjusted eGFR rate of decline varied between 0.8 and 2.7 ml/min/year over a median follow-up of 2 years, with male gender and diabetic status being associated with the highest rates of decline[53]. Furthermore, this study showed that the majority of subjects had a mean eGFR change of 5 ml/min or less, independently from the baseline eGFR. Results from the Cardiovascular Health Study indicated that deterioration in kidney function (increase in serum creatinine > 0.3 mg/dl) was seen in less than 3% of the subjects (mean age 73 years), after a follow-up of at least 3 years[54]. Although these data emphasize the indolent nature of CKD progression in the elderly, we cannot ignore that there is a subset of high-risk patients in whom significant progression is foreseen by the presence of diabetes, substantial proteinuria and lower baseline eGFR (< 30 ml/min)[53,55].

Shlipak *et al.*[56] showed that serum cystatin C-based eGFR detected significantly larger declines in kidney function than creatinine-based formulas in the elderly. In a cohort of 4 380 participants over the age of 65 years, with a maximum follow-up of 7 years, these investigators detected a mean eGFR loss of 0.4 and 1.8 ml/min with creatinine- and cystatin C-based eGFR, respectively (P < 0.001). A rapid decline in eGFR (> 3 ml/min/year) was significantly more common with cystatin C- (25%) than with creatinine-based eGFR (16%). The remaining issue is how this higher eGFR decline identified by cystatin C-based formulas eventually correlates with significant clinical outcomes, as ESRD.

CREATININE-BASED EGFR EQUATIONS AS PREDICTORS OF CLINICAL OUTCOMES

Delaying the progression of kidney dysfunction has been one of the clinical targets when managing CKD patients, as it would result in a reduction of the incidence of ESRD. Nonetheless, one should remember that while CKD progresses with time, the chance of death also increases, particularly in the elderly. Hence, when studying the behaviour of eGFR formulas as predictors of ESRD, we have to bear in mind that, inevitably, we also need to consider death as a competitive event.

This point was nicely evaluated within the American Veteran Affairs cohort of about 210 000 subjects with CKD stages 3-5 at baseline (determined by the MDRD equation), predominately male (only 3% women) and old (83% over the age of 65 years), followed for a mean of 3.2 years[57]. This study showed that the level of eGFR below which the risk of ESRD exceeded the risk of death varied with age, ranging from 45 ml/min for 18-44 year-old to 15 ml/min for 65-84 year-old patients. A shift from the uniform stage-based approach in managing CKD to a more individualized one, in which age would be considered a major effect modifier, was called for.

Matsushita *et al.*[39] analyzed simultaneously different hazard outcomes as ESRD and death, comparing reclassification groups resulting from the application of the two main SCr-based eGFR equations: MDRD and EPI. They showed that EPI equation improved eGFR prediction ability for all-cause and cardiovascular mortality, and ESRD in comparison to MDRD equation, although, after stratifying for age, that improvement in subjects older than 65 years remained only for mortality but not for ESRD prediction.

However, we should not forget that SCr close correlation with the muscle mass is a shortcoming when considering its accuracy as kidney function marker, particularly in populations with important sarcopenia, as the elderly. When considering CKD progression by SCr-based eGFR tertiles as a predictor of mortality in a group of around 15 000 subjects with CKD stages 3-5 at baseline (using SCr-only EPI formula) followed for a median of 3.4 years, investigators found that those subjects in the lower (declining) and upper (increasing) eGFR tertiles had a significantly higher risk of death than those in the middle (stable) tertile, if only patients over the age of 60 years were considered[58]. This rather counter-intuitive observation seemed associated with longitudinal changes in nutritional status (as evaluate by body mass index and serum albumin decrease), that

were significantly more severe in the upper (increasing) eGFR tertile.

CYSTATIN C-BASED EGFR EQUATIONS AS PREDICTORS OF CLINICAL OUTCOMES

Chronic kidney disease progression in the elderly seems to be more significant when cystatin C-based formulas are considered[56]. Similarly, cystatin C has been shown to be a better predictor of morbimortality in CKD patients than SCr. In a cohort of close to 5 200 subjects, with a mean age of 72 years, followed for an average 12.2 years, CKD was considered if eGFR below 60 ml/min using EPI SCr- or cystatin C-based formulas[59]. Risk of death (all-cause or cardiovascular) was significantly higher in patients with CKD defined only by cystatin C-based formulas but not in those with CKD defined only by SCr-based equation[59]. CKD status was associated with ESRD prediction, irrespective of the marker used, although the risk of ESRD in patients with CKD defined only by cystatin C-eGFR was more than double the risk of those with CKD defined only by SCr-eGFR[59].

In a meta-analysis of 11 general and 5 CKD-only populations, including almost 94 000 subjects with about 8 years follow-up, it was demonstrated that GFR estimated by cystatin C alone or in combination with SCr was a stronger predictor of death or ESRD than SCr-alone eGFR, particularly in participants over 65 years[60]. It was also shown that, in subjects over the age of 65 years, cystatin C-based eGFR returned a lower GFR estimate than SCr-based eGFR, in contrast with what was seen in the overall population.

CONCLUSIONS

Any endogenous kidney function marker has limitations. Understandably, eGFR formulas derived from them will present similar drawbacks. The close relationship between muscle mass and SCr accounts largely for the inaccuracy of this marker in the elderly, with cystatin C presenting a better performance as GFR estimator. Even so, SCr is a much widely used marker, and the new EPI formula seems to improve significantly GFR estimation in subjects with no or mild kidney dysfunction, without jeopardizing eGFR performance in subjects with advanced CKD. Its use, particularly in the epidemiological setting, has proven to be useful in identifying subjects with a more relevant CKD (i.e., reduction of kidney function but also with high comorbidity and more prone to CKD progression), selecting those that would profit more from specific interventions (as referral to a nephrologist). Nevertheless, growing evidence has shown cystatin C to be a stronger predictor of clinical outcomes, as death and ESRD, than SCr in the elderly. This observation illustrates the usefulness of cystatin C in the elderly with CKD, in whom important decisions about CKD management and ESRD preparation have to be considered, as it may allow us to better predict CKD progression and appreciate the competitive ESRD versus death risk.

Conflict of interest statement: Nothing to declare.

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