Assessing renal function – searching for the perfect marker continues!

Commentary on

Markers of kidney function in the elderly in relation to the new CKD-EPI formula for estimation of glomerular filtration rate

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Arch Med Sci 2011; 7, 4: 658-664

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Submitted: 21 July 2011
Accepted: 13 August 2011

Arch Med Sci 2011; 7, 4: 565-567
DOI: 10.5114/aoms.2011.24120

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Serum creatinine, as a marker of renal function, continues to be used in spite of inaccuracies in its measurement as well as interference from other factors. This has resulted in a multitude of formulae for calculating the glomerular filtration rate (GFR). More recently, The National Kidney Foundation Dialysis Outcome Quality Initiative (K/DOQI) and the European Best Practice Guidelines recommended the use of the Modification of Diet in Renal Disease (MDRD) study population for reporting estimated GFR (eGFR) [1-3]. This is in preference to other formulae previously used to estimate renal function [4]. However, many of the shortcomings associated with eGFR calculation persist and the search for an ideal marker of renal function continues.

The clearance of exogenous markers such as inulin ("gold standard" method) and synthetic poly fructose solutions as well as non-radioactive contrast media such as iohexol are considered as a more accurate evaluation of renal function [5]. Measurement of creatinine has suffered in the past from inter-laboratory differences, some of which are attributed to differences in calibration [6]. In addition, the measurement of creatinine by the most common method (Jaffé) is subject to interference by chromogens such as bilirubin, glucose and uric acid. Similarly, the enzymatic method is prone to interference by bilirubin and some antibiotics. Serum creatinine measurement is also influenced by factors such as creatinine turnover rate, tubular secretion of creatinine and creatinine production rate, which is reflected by the muscle mass [7]. Some studies have shown that administration of cimetidine to block tubular secretion improves the reliability of GFR measurement [8]. Some uniformity with measurement has been introduced by adoption of a common calibration to isotope dilution mass spectrophotometry standard with substantial improvement and traceability for creatinine measurements [9]. Larger muscle mass in Afro-Caribbeans and smaller muscle mass in South Asians would show variable renal function compared with renal function measured by gold standard methods if not corrected for muscle mass [7].

Renal function deteriorates by 8 ml/min per decade, in the ageing population, but there is also wide intra-individual variability in this group [10-12]. Although the loss of renal parenchyma with ageing accounts for this change, sarcopenia seen in the elderly resulting in reduction in creatinine production also influences renal function measurement [13]. Muscle mass declines by 1-2% per year after 50 years. There is also an age-related reduction in total body water, but a higher mass of body fat. Muscle strength declines by 1.5% per year from age 50 to 60 years and after 60 years [14, 15]. Lower creatinine levels have been reported in subjects with vitamin D deficiency [16]. Vitamin D deficiency is common among South Asians in the UK and this may also increase the rate of loss of muscle mass in this population along with a decrease in muscle strength [16]. The prevalence of vitamin D deficiency is also higher in the elderly. True renal function measurements are essential in the elderly population where these and other age-related changes alter the pharmacokinetics of pharmaceutical agents used for therapy or diagnosis leading to iatrogenic toxicity. This may also be true for the group of subjects who have been shown to have a smaller muscle mass and higher body fat, such as those from South Asian countries.

There has been an interest in using low molecular weight proteins such as β_2-microglobulin and cystatin C as markers of renal function. Cystatin C, a protein that is produced by all the nucleated cells, has been shown to be superior to creatinine as a maker of renal function with > 92% identity with reference tests for GFR [17, 18]. Cystatin C level is independent of age, nutrition, diet (e.g. exogenous creatinine from meat-rich diet), gender and interference with creatinine measurement (e.g. bilirubin) [18]. Equations have also been developed using cystatin C measurements for estimating eGFR [19]. However, cystatin C is not a perfect marker, being influenced by infection, hypo- or hyperthyroidism or drugs such as corticosteroids, angiotensin-converting inhibitors, calcineurin inhibitors and co-trimoxazole [18]. Larger intra-individual variation has also been reported with cystatin C. Moreover, cystatin measurements are not standardised and expensive compared with creatinine measurement.

The inherent problems in using the different prediction equations stem from the problems associated with the selected population used for deriving the equation as well as the analytical problems associated with measurement of creatinine or cystatin C. The globally adopted MDRD equation was derived from subjects who had renal impairment and the GFR measured by iothalamate was 40 ±21 ml/min/1.73 m^2 (mean ± SD) aged between 18 and 70 years (mean age ± SD: 51 ±13 years) [3]. Subjects less than 80% of ideal weight and above 160% of ideal weight were excluded [3]. The study also did not recruit subjects of diverse ethnicity. Therefore, extrapolating this prediction for measuring eGFR to different ethnic and age groups should be viewed with caution. In a screening study [20, 21] involving a Gujarati population (currently n = 1267) we noted a significant discrepancy in measurement of eGFR in using different prediction equations in relation to higher body fat (measured by 4 point bioelectrical impedance) (unpublished results). The MDRD formula also underestimates eGFR in those with normal renal function as well as in the paediatric age group, pregnant women, amputees, subjects with very high body mass index and those aged > 70 years [3].

Recently, there has been an interest in assessing the use of neutrophil gelatinase-associated lipocalin (NGAL) (which functions as a shuttle for iron and siderophores) as a marker of renal function [22]. NGAL is a small 25-kD protein released from renal tubular cells. Several studies have reported that NGAL may become a novel marker for impaired renal function. Serum and urine NGAL levels show impressive predictive power for progression of chronic kidney disease (CKD). The NGAL is released from the renal tubule soon after damage even before the circulating creatinine level rises. A recent study has validated its specificity as an early predictor of acute kidney injury [23]. Many of the factors that influence creatinine measurements will not affect the measurements of NGAL [23], with the possible exception of pregnancy [24].

In this issue of the journal, Malyszko and colleagues measured NGAL, kidney injury molecule-1 (KIM-1) and cystatin C in 412 subjects to assess the prevalence of CKD [25]. Renal function was assessed by the MDRD, Cockcroft-Gault and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations. The NGAL was the best predictor for eGFR in those below and above 65 years. These findings need to be evaluated using a gold standard method. Their finding that diabetic patients had a higher level of NGAL than the non-diabetic patients but with very similar creatinine levels is very interesting and may help predict future eGFR values. They [25] also reported that the normotensive elderly had lower NGAL compared with hypertensive subjects with similar serum creatinine levels. Therefore, NGAL holds some promise as a marker for predicting renal impairment and there is potential for its use to assess reversal of renal impairment after treatment. Another marker of proximal tubular origin, KIM-1, has been shown to be raised in ischaemic toxic injury to the kidney [25]. The KIM-1 (a transmembrane protein with immunoglobulin like mucin domains in its ectodomain) is completely absent in kidneys

without any evidence of damage [24]. Urinary excretion of KIM-1 has been shown to be an independent predictor of long-term graft dysfunction after kidney transplant [26]. However, evidence for its use in screening people with CKD is lacking. Other markers may prove useful as therapeutic targets, diagnostic tests or prognostic tools to help prevent kidney damage [27, 28] but they are beyond the scope of the present editorial.

Accurate assessment of renal function is essential especially in those at high risk of developing CKD, both young and old. Screening individuals with the available prediction equations has limitations. New markers of kidney injury such as NGAL hold hopes for improved prediction of renal function independently of age, ethnicity, gender, muscle mass and body fat. More studies are needed to assess the influence of ethnicity, various drugs and changes in body composition in relation to this marker. Until then, use of creatinine in various equations predicting renal function will continue for screening and monitoring.

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