

ORIGINAL ARTICLES

The Relationship Between Serum Creatinine and Estimated Glomerular Filtration Rate: Implications for Clinical Practice

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ABSTRACT

Introduction

A new classification of chronic kidney disease (CKD) has been widely adopted that stratifies patients into 5 'stages' according to estimated glomerular filtration rate (eGFR). In adults the most commonly used formulae to calculate eGFR are the Cockcroft and Gault (C&G) and Modification of Diet in Renal Disease (MDRD) formulae. The UK Renal Association has recommended calculation of MDRD eGFR to screen for reduced kidney function in primary and secondary care.

Aim

The aim of this study was to explore the implication of using these predictive formulae.

Methods

We searched for patients currently attending a renal clinic who have ever had a serum creatinine (SCr) of exactly 100 mol/L, 150 mol/L or 200 mol/L. The C&G and MDRD eGFRs corresponding to that SCr were calculated. The proportion of patients in each stage of the CKD classification was determined.

Results

For a SCr of 100 mol/L mean eGFR was 86.5ml/min (range 31.0 - 192.8) by C&G and 63.8ml/min (range 39.7 - 99.9) by MDRD ($p < 0.0001$; t-test of mean). For SCr 150 mol/L mean eGFR was 51.7ml/min (18.0 - 110.4) by C&G and 38.0ml/min (20.7 - 54.8) by MDRD ($p < 0.0001$). For SCr of 200 mol/L mean eGFR was 34.4ml/min (12.6 - 89.5) by C&G and 27.3ml/min (16.7 - 41.3) by MDRD ($p < 0.0001$). Using MDRD eGFR 46.5% patients with a SCr of 100 mol/L have stage 3 CKD (GFR 30-60ml/min) and all patients with a SCr of 150 mol/L or 200 mol/L have CKD 3 or worse. 8.6% of males with SCr 100 mol/L had stage 3 CKD or worse compared with 86.8% females. 70.2% patients > 65 years old with SCr 100 mol/L had stage 3 CKD.

Conclusions

Targeted screening of patients at-risk for CKD will identify a large number of patients who require management of CKD and potential referral to nephrology services even at levels of SCr regarded as 'normal' or mildly elevated. This will apply especially to elderly patients and females.

Introduction

In the last few years it has become increasingly recognised that what was previously thought to be 'mild' impairment of kidney function is associated with an increased risk of cardiovascular events.¹ In this context a new classification of chronic kidney disease (CKD) has been widely adopted (Table I) that attempts to stratify patients according to risk and need for interventions.² In the last three years the National Kidney Foundation in the USA, the European

Table I Classification of chronic kidney disease (CKD). Adapted from the National Kidney Foundation K/DOQI clinical practice guidelines for chronic kidney disease²

Stage 1	Normal GFR; GFR >90 mL/min with other evidence of chronic kidney damage*
Stage 2	Mild impairment; GFR 60-89 mL/min with other evidence of chronic kidney damage**
Stage 3	Moderate impairment; GFR 30-59 mL/min
Stage 4	Severe impairment; GFR 15-29 mL/min
Stage 5	Established renal failure (ERF): GFR < 15mL/min or on dialysis

* The "other evidence of chronic kidney damage" may be one of the following: persistent microalbuminuria; persistent proteinuria; persistent haematuria (after exclusion of other causes, e.g. urological disease); structural abnormalities of the kidneys demonstrated on ultrasound scanning or other radiological tests, e.g. polycystic kidney disease, reflux nephropathy; biopsy-proven chronic glomerulonephritis (most of these patients will have microalbuminuria or proteinuria, and/or haematuria)

** Patients found to have a GFR of 60-89 mL/min/1.73 m² without one of these markers should not be considered to have CKD and should not be subjected to further investigation unless there are additional reasons to do so.

Best Practice Guidelines and the UK Renal Association have all recommended the use of estimated glomerular filtration rate (eGFR) rather than serum creatinine (SCr) to assess and monitor kidney function.^{2,3,4} Furthermore, the UK Renal Association has recommended the use of eGFR to screen at-risk patients for reduced kidney function in primary and secondary care and that all biochemistry laboratories report eGFR alongside SCr.⁴

Glomerular filtration rate (GFR) is the best measure of kidney excretory function. Direct measurement of GFR is impractical for routine clinical practice. Calculation of creatinine clearance from a SCr concentration and 24 hour urine creatinine measurement is often used as an estimate of GFR but is too cumbersome and inaccurate for widespread monitoring. For this reason SCr concentration is usually used to estimate kidney function. Creatinine is a metabolic product of creatine and phosphocreatine, both of which are found almost exclusively in muscle.⁵ SCr concentration is inversely proportional to GFR and directly proportional to muscle bulk and dietary protein intake.⁶ The clinician must therefore take the patient's

muscle bulk in to account when considering how the SCr relates to GFR in an individual patient. Several authors have suggested the use of mathematic formulae to predict GFR. In large populations these methods show correlations with the gold standard but they can lead to inaccuracy in individual subjects. In adults the most commonly used formulae are the Cockcroft and Gault formula (C&G) which uses SCr, age, sex and weight⁷ and the MDRD formula which was derived from data collected in the Modification of Diet in Renal Disease (MDRD) study⁸ and gives an estimate of GFR based on age, sex, race, serum urea, SCr and serum albumin. By avoiding the need for patient weight the MDRD formula is less prone to errors related to fluid overload, obesity and limb amputation all of which can adversely affect the accuracy of the C&G formula.

The aim of this study was to explore further the implication of using these predictive formulae by analysing the estimated glomerular filtration rate (eGFR) in adult patients who had a SCr of exactly 100, 150 or 200 $\mu\text{mol/L}$ during follow up at the renal clinic in a single centre. We chose these values because 100 $\mu\text{mol/L}$ is in the middle of the usually quoted 'normal' range for SCr, 150 $\mu\text{mol/L}$ is the upper limit of the reference interval for SCr in the Oxford Handbook of Clinical Medicine,⁹ and has previously been used as a threshold of kidney damage in management guidelines^{10,11} and, in our experience, 200 $\mu\text{mol/L}$ is often perceived to be 'mild' kidney failure.

Methods

All patients attending the Renal Unit of the Western Infirmary, Glasgow are included in the Renal Unit database. Clinical data are entered prospectively at each attendance and data are transferred automatically from relevant laboratories. We performed a search for all patients who are currently attending a general renal clinic and have ever had a SCr of exactly 100 $\mu\text{mol/L}$, 150 $\mu\text{mol/L}$ or 200 $\mu\text{mol/L}$. Once identified, the C&G and MDRD eGFRs corresponding to that SCr were calculated. Patient sex and age were also recorded.

The C&G formula is:

$$\text{eGFR} = \left[\frac{(140 - \text{age}) \times 1.2}{\text{SCr}} \right] \times (0.85 \text{ if female})$$

Where age is expressed in years, SCr in $\mu\text{mol/L}$ and weight in kg.

The MDRD formula is:

$$\text{eGFR} = 170 \times (\text{SCr}/88.4)^{-0.999} \times \text{age}^{-0.176} \times (\text{SU}/0.357)^{-0.170} \times (\text{SAlb} \times 10)^{+0.318} \times (0.762 \text{ if female}) \times (1.180 \text{ if black})$$

Where SCr = serum creatinine in $\mu\text{mol/L}$, SU = serum urea in mmol/L, SAlb = serum albumin in g/L and age is expressed in years.

The means, standard deviations, medians, inter-quartile ranges and absolute ranges of eGFR were compared. The proportion of patients in each stage of the CKD classification was determined, with sub-analyses by sex and age. Patients with transplants and patients on dialysis were excluded to ensure that the SCr of interest related to native kidney function alone.

Statistics

Boxplots were created for visual comparison using SPSS for Windows v13.0. Comparison of mean eGFR between C&G and MDRD formulae and by sex was by unpaired t-test with $p < 0.05$ being regarded as statistically significant. Statistical calculations were done using SPSS for Windows v13.0.

Results

549 patients with SCr of 100 $\mu\text{mol/L}$, 305 with SCr of 150 $\mu\text{mol/L}$ and 196 with SCr of 200 $\mu\text{mol/L}$ were identified. For simplicity only the 187 patients with SCr of 100 $\mu\text{mol/L}$ since the beginning of 2003 were included. This left a total of 688 patients. The mean ages of the patients with SCr of 100 $\mu\text{mol/L}$, 150 $\mu\text{mol/L}$ and 200 $\mu\text{mol/L}$ were 55.2, 60.5 and 64.0 years respectively. The proportions of males in the groups with SCr of 100 $\mu\text{mol/L}$, 150 $\mu\text{mol/L}$ and 200 $\mu\text{mol/L}$ were 49.7%, 60.0% and 53.1% respectively. Calculation of eGFR by C&G requires a measure of patient weight; this is recorded at each clinic visit but the SCr measurement of interest may not have been at the time of a clinic visit. Calculation of eGFR by MDRD requires a measure of serum albumin and the patient may not have had a measurement of serum albumin at the same time as the SCr of interest. Therefore C&G estimates were available for 383 patients (55.6%), and MDRD estimates were available for 575 patients (83.6%). The number of measures of C&G eGFR and MDRD eGFR for each level of SCr are shown in Table II.

The results for the whole study sample are summarised in Table II. The mean C&G eGFR was consistently higher than the mean MDRD eGFR and the range was wider using the C&G formula: for a SCr of 100 $\mu\text{mol/L}$ the mean eGFR was 86.5 ml/min (range 31.0 – 192.8) by C&G and 63.8 ml/min (range 39.7 – 99.9) by MDRD ($p < 0.0001$; t-test of mean). For a SCr of 150 $\mu\text{mol/L}$ the mean eGFR was 51.7 ml/min (range 18.0 – 110.4) by C&G and

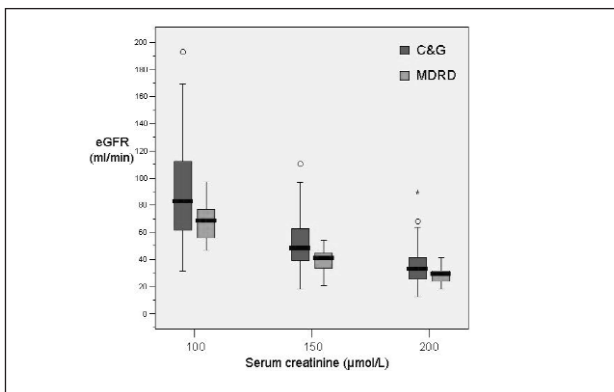
Table II. Summary data. Cockcroft and Gault formula (C&G) or MDRD formula eGFR (mL/min) for patients with SCr of exactly 100 µmol/L, 150 µmol/L or 200 µmol/L

SCr (µmol/L)	100		150		200	
	C&G n=80	MDRD n=157	C&G n=183	MDRD n=258	C&G n=120	MDRD n=160
Minimum	31.0	39.7	18.0	20.7	12.6	16.7
Maximum	192.8	99.9	110.4	54.8	89.5	41.3
Median	80.55	63.8	49.2	39.3	31.8	27.6
First quartile	61.38	52.9	39.5	32.9	25.2	23.4
Third quartile	110.65	73.8	62.7	44.2	41.4	31.0
Mean	86.5	63.8	51.7	38.0	34.4	27.3
Standard deviation	32.5	12.4	17.3	6.9	12.9	4.9

38.0ml/min (range 20.7 – 54.8) by MDRD ($p < 0.0001$; t-test of mean). For a SCr of 200 µmol/L the mean eGFR was 34.4ml/min (range 12.6 – 89.5) by C&G and 27.3ml/min (range 16.7 – 41.3) by MDRD ($p < 0.0001$; t-test of mean). The spread is illustrated in the boxplot in Figure 1.

The proportion of patients in each stage of the new CKD classification is shown in Figure 2. Using the MDRD

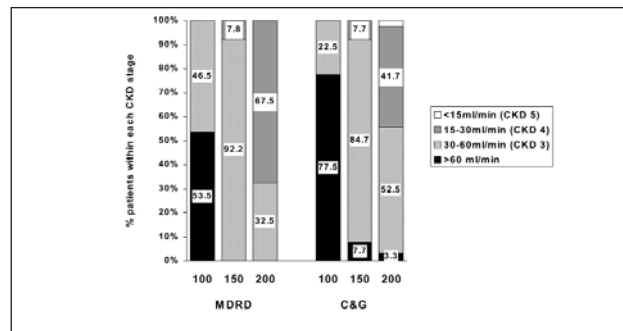
Figure 1 Boxplot of of MDRD and C&G eGFR for patients with SCr of exactly 100 µmol/L, 150 µmol/L and 200 µmol/L illustrating median (thick horizontal line), interquartile range and full range with outliers



eGFR 46.5% patients with a SCr of 100 µmol/L have stage 3 CKD (GFR 30-60ml/min) and all patients with a SCr of 150 µmol/L or 200 µmol/L have CKD 3 or worse. Furthermore 7.8% of patients with SCr 150 µmol/L and 67.5% of patients with SCr 200 µmol/L have stage 4 CKD (GFR 15-30ml/min). Using the C&G formula a slightly lower proportion of patients is classified as having CKD stage 3 or worse (Figure 2).

As expected the mean eGFR was consistently higher in males than females. Using the MDRD formula for patients with SCr 100 µmol/L mean eGFR was 72.6ml/min for males v 54.4ml/min for females ($p < 0.0001$); for

Figure 2 Proportion of patients with serum creatinine of exactly 100 µmol/L, 150 µmol/L or 200 µmol/L within each stage of the new classification of CKD using MDRD or C&G formulae to calculate eGFR.

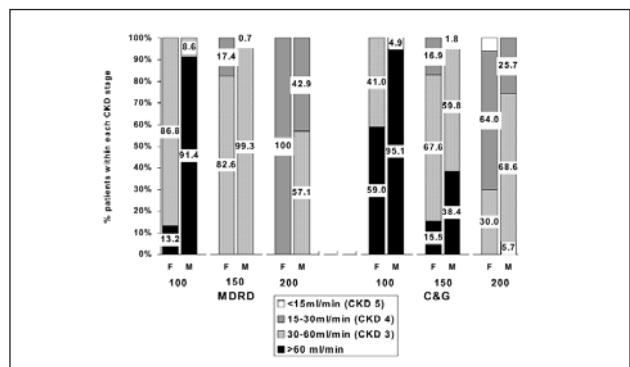


patients with SCr 150 µmol/L mean eGFR was 43.5ml/min for males v 32.7ml/min for females ($p < 0.0001$); and for patients with SCr 200 µmol/L mean eGFR was 30.7ml/min for males v 23.3ml/min for females ($p < 0.0001$).

The impact of sex on eGFR is shown in Figure 3. Using the MDRD formula 91.4% of males with SCr 100 µmol/L have eGFR >60ml/min compared with only 13.2% females. Similarly all females with SCr 200 µmol/L had stage 4 CKD (GFR 15-30ml/min) compared with only 42.9% males. The impact of sex on C&G eGFR was similar.

As expected patients with advancing age had lower eGFR for any of the 3 levels of SCr. The impact of age on eGFR

Figure 3 Proportion of females (F) and males (M) with serum creatinine of exactly 100 µmol/L, 150 µmol/L or 200 µmol/L within each stage of the new classification of CKD using MDRD or C&G formulae to calculate eGFR.



is illustrated in Figure 4 which shows the proportion of patients in each CKD stage in the subset of patients > 65 years ($n=254$ for MDRD formula and $n=157$ for C&G formula) at the time of the SCr measurement. Using the MDRD formula 70.2% patients > 65 years with SCr 100 µmol/L have CKD stage 3 (eGFR 30-60ml/min). Furthermore 16.1% patients >65 years with SCr 150 µmol/L and 79.8% with SCr 200 µmol/L have CKD stage 4 (eGFR 15-30ml/min). The impact of age on C&G eGFR was similar; 3 patients >65 years with SCr

200 μ mol/L were found to have stage 5 CKD (GFR < 15 ml/min).

Discussion

Our data show that for any level of SCr the range for eGFR is wide. The range of eGFR measures is greater when using the C&G formula than the MDRD formula. Furthermore, even with an apparently 'normal' SCr (100 μ mol/L) almost 50% of patients will be classified as CKD stage 3. Analysing patients with exactly the same SCr illustrates the wide inter-individual variability of SCr as a measure of kidney function and the fact that a substantial proportion of patients with SCr in the laboratory quoted "normal" range have significantly reduced kidney function. This is especially true for females and patients with advancing age.

It is no surprise that males have a higher eGFR for a given SCr, or that younger patients have a higher eGFR than older patients since sex and age are included in the formulae to calculate eGFR. The design of our study demonstrates the implications for assessing kidney function, however, in a secondary care setting.

The results are not applicable only to patients attending a renal clinic: any population with the same age, sex, race and weight distribution will have the same distribution of eGFR for any given serum creatinine concentration because age, sex, race and weight are the dominant variables in the formulae. Recent guidelines suggest that in routine clinical practice kidney function should be assessed by formula-based estimates of GFR (eGFR) and that laboratories should report eGFR using the MDRD formula whenever SCr is measured.^{2,3,4} This guidance has been linked to the new classification of chronic kidney disease and the observation that even mild reductions in GFR are associated with increased risks of morbidity and mortality.¹

UK guidelines recommend that patients with CKD stage 3 should have a management plan that includes attention to cardiovascular risk factors, assessment of urine protein excretion, haematuria, renal osteodystrophy and anaemia, regular follow-up and consideration for referral to a nephrologist.⁴ Patients with CKD 4 and 5 should be managed in conjunction with local nephrology services in addition to the interventions described for CKD stage 3.

The recommendation that eGFR is the best way to assess kidney function is based on the fact that only a blood

sample is required and that previous studies have validated these formulae. The C&G formula was first developed in a study of 236 adult males with near-normal kidney function using SCr, age, sex and weight to predict measured creatinine clearance rather than measured GFR.⁷ It was subsequently modified for females simply by multiplying by a factor of 0.85 based on other studies available at the time.^{12,13,14} The C&G formula tends to overestimate true GFR by as much as 16% when compared with inulin clearance, the gold standard for GFR measurement.⁸ C&G substantially overestimates GFR in patients who are obese and fluid overloaded as the fat and fluid contributions to the body weight are incorrectly 'credited' as muscle.¹⁵ This probably explains the higher mean eGFR measured by C&G compared with MDRD in our study. C&G has been shown to be particularly inaccurate among younger individuals whose measured GFR was greater than 60 ml/min.¹⁶

The MDRD formula was developed more recently using stepwise regression analysis to predict measured GFR (corrected for body surface area) in a sample of 1070 patients enrolled in the Modification of Diet in Renal Disease study.⁸ The formula uses SCr, age, sex, ethnicity, serum urea and serum albumin to calculate eGFR. The fact that weight is not included in this formula reduces errors associated with obesity, fluid overload and amputations. As the contribution of serum urea and albumin to the final equation were found to be relatively minor, a simplified 4-variable MDRD formula has been widely adopted¹⁷ although we used the 6 variable version in our study. Subsequent studies have raised concern about the accuracy of the MDRD formula in specific groups of patients; the MDRD formula has been shown to overestimate GFR in those with advanced chronic kidney failure, and underestimate it in Chinese patients with mild chronic kidney failure.¹⁸ In a study of patients with chronic kidney disease but normal SCr only 24% of MDRD eGFR results were within 30% of measured GFR.¹⁹ The MDRD formula has not been validated in those without kidney disease, those with diabetes or those with serious comorbidities.

Several studies have compared C&G and MDRD directly; one showed that GFR was overestimated by 2 ml/min using C&G and underestimated by 1 ml/min by the MDRD formula,²⁰ and another showed that in patients with GFR of less than 60 ml/min (measured by ¹²⁵I-iothalamate clearance) C&G overestimated GFR by 3.5 ml/min and MDRD underestimated it by 0.5 ml/min.²⁰

These previous observations raise concern that the eGFR may not be an accurate reflection of true GFR in the patients with SCr 100 μ mol/L in our study and that some patients may be diagnosed as having CKD stage 3 or worse who do not have kidney disease. This may not be a bad thing since most of the interventions suggested for these patients (life-style measures to reduce cardiovascular risk, control of hypertension, cholesterol lowering) are safe and inexpensive; it may be, however, that the diagnosis of reduced kidney function is associated with unnecessary anxiety for an individual patient.

The widespread implementation of eGFR reporting by biochemistry laboratories in UK will provide important information regarding the prevalence of reduced kidney function in targeted populations in primary and secondary care. It is likely this will lead to refinement of the formulae used to derive eGFR and of the screening and treatment plans that have been proposed.

Conclusion

This study highlights the implications of adopting the recommendation to report eGFR alongside measures of SCr. Our data suggest that targeted screening of patients at-risk for CKD will identify a large number of patients who require management of CKD and potential referral to nephrology services even at levels of SCr regarded as 'normal' or mildly elevated. This will apply especially to elderly patients and to females. Further studies are needed to determine whether modification of the recommended MDRD formula is required at higher levels of kidney function. Clinicians in primary and secondary care need to become familiar with formula-based eGFR. Despite the resource implications the recent guidance to identify patients with significantly reduced kidney function by targeted screening has the potential to substantially reduce morbidity and mortality with the adoption of relatively simple cardiovascular risk reduction interventions.

REFERENCES

1. Sarnak MJ, Levey AS. Cardiovascular disease and chronic renal disease: a new paradigm. *Am J Kidney Dis.* 2000; 35(suppl 1): S117–S131
2. Kidney Disease Quality Outcome Initiative clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis.* 2002; 39(2 Suppl 2): S1–246
3. European Best Practice Guidelines for Haemodialysis. Section 1. Measurement of renal function, when to refer and when to start dialysis. *Nephrol Dial. Transplant* 2002; 17 (Suppl 7): S7–S15
4. Chronic Kidney Disease in Adults: UK Guidelines for Identification, Management and Referral of Adults. Available at http://www.renal.org/CKDguide/full/Recommendations.htm#_Toc84317968 (Accessed 15th November 2005)
5. Wyss M., Kaddurah-Daouk R. Creatine and creatinine metabolism. *Physiol Rev.* 2000; 80: 1107–1213
6. Lew SW, Bosch JP. Effect of diet on creatinine clearance and excretion in young and elderly healthy subjects and in patients with renal disease. *J Am Soc Nephrol* 1991; 2: 856–865
7. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976; 16: 31–41
8. Levey AS, Bosch JP, Lewis JB et al. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. *Ann Intern Med* 1999; 130: 461–470
9. Longmore M, Wilkinson I, Torok E (eds). *Oxford Handbook of Clinical Medicine.* Oxford: Oxford University Press, 2001. p716
10. Scottish Intercollegiate Guidelines Network (SIGN) Management of diabetes. Guideline 55 Edinburgh: Sign, 2001. Available at <http://www.elib.scot.nhs.uk/portal/upload/sign55.pdf> (Accessed 14th November 2005)
11. Scottish Intercollegiate Guidelines Network (SIGN) Hypertension in older people. Quick Reference Guide. Guideline 49. Edinburgh: SIGN, 2000. Available at <http://www.sign.ac.uk/pdf/qrg49.pdf>. (Accessed 14th November 2005)
12. Edwards KD, Whyte HM. Plasma creatinine level and creatinine clearance as tests of renal function. *Australas Ann Med* 1959; 8: 218–224
13. Jelliffe RW. Estimation of creatinine clearance when urine cannot be collected. *Lancet* 1971; 1: 975–976
14. Kampmann JP, Siersbaek-Nielsen K, Kristensen M, et al. Alderbetingede variationer i urinkreatinin og endogen kreatininclearance *Ugeskr Laeger* 1971; 133: 2369–2372
15. Salazar DE, Corcoran GB. Predicting creatinine clearance and renal drug clearance in obese patients from estimated fat-free body mass. *Am J Med.* 1988; 84: 1053–60.
16. Froissart M, Rossert J, Jacquot C, et al. Predictive performance of the modification of diet in renal disease and Cockcroft–Gault equations for estimating renal function. *J Am Soc Nephrol* 2005; 16: 763–773
17. Manjunath G, Sarnak MJ, Levey AS. Prediction equations to estimate glomerular filtration rate: an update. *Curr Opin Nephrol Hyertens.* 2001; 10: 785–792
18. Zuo L, Ma YC, Zhou YH et al. Application of GFR–estimating equations in Chinese patients with chronic kidney disease. *Am J Kidney Dis.* 2005; 45: 463–472
19. Bostom AG, Kronenberg F, Ritz E. Predictive performance of renal function equations for patients with chronic kidney disease and normal serum creatinine levels. *J Am Soc Nephrol.* 2002; Aug;13: 2140–4
20. Poggio ED, Wang X, Greene T, et al. 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: 459–466