Mini-Review

Estimating Renal Function for Drug Dosing Decisions

Graham RD Jones[1,2]
[1]Department of Chemical Pathology, SydPath, St Vincent's Hospital, Sydney, Victoria St, Darlinghurst, NSW 2010, Australia.
[2]Faculty of Medicine, University of NSW, Sydney, NSW 2052, Australia.
For correspondence: Dr Graham Jones, gjones@stvincents.com.au

Abstract
In order to adjust the dose of renally excreted drugs in response to reduced renal function, it is necessary to make a quantitative estimate of the glomerular filtration rate (GFR) of the patient. Traditionally this has been done with the use of the Cockcroft and Gault equation or a measured creatinine clearance. More recently the MDRD (Modification of Diet in Renal Disease) formula has become available, providing an estimate of GFR readily available on routine pathology reports. The presence of these different methods of assessing renal function has created some confusion for healthcare workers as to the best approach. In this paper the two methods are compared, together with a newer formula CKD-EPI (named after the Chronic Kidney Disease Epidemiology Collaborative), and a proposal is made for future practice.

Introduction
There is advice, for many drugs, that patients with reduced renal function be given a reduced dose. A simplistic model would indicate that if a drug is removed from the body by renal filtration and the GFR is reduced, then the drug may accumulate in the blood producing a greater chance of toxicity. There are however many other changes that occur in kidney disease other than reduced GFR which can affect drug clearance. These include changes in the volume of distribution, changes in albumin concentration, changes in organic acid accumulation and changes in tubular function. The importance of these factors for each drug will differ depending on the metabolic processes affecting that drug. While using an estimate of GFR to aid in drug dosing decisions is the focus of this paper, it is important to remember that there are other important tools to assist with drug dosing decisions such as assessing the patient for signs of efficacy or toxicity, and from therapeutic drug monitoring. These factors are addressed in more detail elsewhere in this issue.[1]

Advice on drug dosing in renal dysfunction is available from many sources. These include the drug package information, MIMs,[2] Therapeutic Guidelines[3] and Australian Medicines Handbook.[4] The advice in these sources is based on some estimate of the GFR of the patient, commonly by way of the Cockcroft and Gault formula (C&G),[5] or a measured creatinine clearance using a 24-hour urine collection together with a blood sample. Strictly these are both estimates of creatinine clearance (eCrCl) which is itself an estimate of GFR. It is of note that the advice given is generally in the form of dose reductions for different eCrCl values based on broad categories of eCrCl. For example dosing for allopurinol is based on categories of >90, 50–89, 10–49 and <10 mL/min. Also many drug dose adjustments are fairly broad depending on the available size of tablets, capsules or other formulations. Against this background it could be considered that an approximate estimation of GFR may be sufficient for most drug dosing decisions, although there are exceptions where alternative monitoring is required.[1]

In contrast to the recommendations of the common drug information sources, in 2007 the Australasian Creatinine Consensus noted that using the eGFR calculated with the MDRD formula was acceptable to assist with drug dosing decisions in some circumstances, for example in general practice with non-critical-dose drugs.[6,7] The rationale for this recommendation was that awareness of a reduced GFR is the first requirement of a decision to reduce a drug dose, and that the eGFR as routinely reported by pathology laboratories provides this information in a direct manner, on every pathology report which includes creatinine, and without the need for additional calculations. As reduced renal function, especially in the elderly, can occur with a serum creatinine concentration within the population reference

intervals, the ready availability of a warning of reduced GFR, albeit imperfect, was considered to be more important than recommending a calculation that may not be performed. This advice has led to some public controversy with criticisms in both Australian[8] and international publications.[9] A statement was also added to the Therapeutic Guidelines statement on dosing in patients with reduced renal function indicating that the 'eGFR commonly reported on pathology reports should not be used for drug dosing decisions' although the 2010 update has softened this to indicate that the MDRD formula has not been validated for this purpose.

My aim in this paper is to consider what may be the most appropriate formula to use for making drug dosing decisions in renal disease. This assessment is made in the awareness that, as indicated above, while reduction in GFR is only one factor of renal disease that may affect drug clearance, all available advice indicates that some estimate of GFR is the most suitable tool for making drug dose adjustment decisions. Therefore for the purposes of this discussion, I will make the assumption that the best formula for drug dosing would be one which best estimates the true GFR in a patient. Putting this another way, if there was uncertainty about the GFR for a drug dosing decision, a formal GFR measurement would be the most suitable tool for resolving the uncertainty.

The Best Equation

The disagreements over the most appropriate formula for GFR estimation can be summarised as 'C&G vs MDRD'. It is my belief that the disparate advice regarding these two unrelated methods for estimating GFR has been detrimental to the vital message that some drugs need to have doses reduced in renal failure. For example, a discussion on this topic often requires a careful explanation of the different formulae and their strengths and weaknesses, rather than focusing on the wider issue of how to respond to the changes in GFR. However, it should be noted that results from the two formulae are not interchangeable. Especially in the elderly, results generated from MDRD tend to be significantly higher than those from the C&G equation and thus would often lead to a higher drug dose being prescribed. The magnitude of the scatter between the two estimates of GFR is shown in Figure 1A where results for MDRD are plotted against C&G for 32,000 Australians presenting to a routine pathology service.[10] It can be seen that the choice of equation produces different results in many patients and consequently potential differences in treatment.

Both the MDRD formula and C&G are based on measurement of serum creatinine and thus both are subject to some of the same limitations such as assay interferences and rapidly changing renal function. Each equation uses a relationship of 1/serum creatinine (or close to it in the case of the MDRD formula) reflecting the approximately hyperbolic relationship between serum creatinine and GFR. The other significant unknown is the rate of creatinine production which is proportional to muscle mass. Thus the other inputs to the equations are designed to provide an estimate of the muscle mass of the patient based on available information.

Cockcroft and Gault Formula

The C&G formula was developed in 1976 from 249 people (approximately 96% male) and has subsequently been 'validated' in at least 58 studies.[11] Limitations to these studies include the use of unstandardised creatinine assays and differing reference materials. C&G is an estimate of measured creatinine clearance where the patient's age, sex and weight are used to estimate the 24-hour creatinine output which is then inserted in a standard clearance calculation (i.e. urine concentration x urine volume output per time / plasma concentration). The results are expressed in mL/min. The original paper shows a variability in the eCrCl compared with measured creatinine clearance (based on the average of two measurements) with about 80% within +/- 30% of the measured creatinine clearance value. The assumption behind this formula is that muscle mass, as reflected by the creatinine output, is a definite percentage of the patient's body weight that falls in a linear manner as the patient ages.

The C&G formula is based on a creatinine assay from 1976 for which the details are no longer available. It has since been widely used with assays which are not directly comparable with each other, let alone with the assay used in the original study. Since the introduction of standardised creatinine assays,[12] measured creatinine values have generally fallen, especially so within the reference interval. This has led to an increase in the eCrCl by a variable amount depending on the standardisation of the previous assay. Following assay standardisation eCrCl results from different laboratories should be more closely aligned with each other. However, there is no revised version of the formula developed for standardised creatinine assays. Anecdotally it was previously claimed that the over-estimation of serum creatinine had the serendipitous effect of cancelling out the positive bias of creatinine clearance compared with GFR, giving a more accurate estimate of GFR. This effect has been removed by the introduction of creatinine assays standardised with isotope dilution mass spectrometry (IDMS).

There is variation in the implementation of the C&G formula based on concerns about the relative amount of muscle mass in very heavy people, where fat is likely to be the major contributor to body mass. There are recommendations to use

ideal body weight (IBW) in place of actual body weight, with IBW estimated from the patient height. There is however variability in the use of this adjustment, with MIMs recommending actual weight, Therapeutic Guidelines the IBW if obese (or if 'morbidly obese' in the 2010 revision), and Australian Medicines Handbook the lower of actual weight and IBW. The differences in eGFR caused by the choice of formula are not insignificant as shown in Fig 1B where, for example, a C&G with actual body weight of 60 mL/min may give values between 30 and 80 mL/min using IBW. While IBW correction is commonly used, there is evidence that this correction does not provide an optimal estimate of the GFR[13,14] and its use should be questioned.

In summary, when it comes to providing an estimate of the GFR, the C&G formula suffers many faults due to lack of robust validation with current assays and lack of traceability to formal GFR measurements, and it has generally been found to perform more poorly than other methods.[15] With regard to drug dosing decisions in practice, it also has the limitation of requiring an active process to perform the calculation in order to make an assessment of the renal function.

MDRD Formula

The MDRD formula was developed in over 1600 subjects, most with renal failure, as part of a process to provide robust tools for a study into dietary intervention in renal disease.[7] While it is known to have significant limitations, including over 10% of results deviating more than 30% from those derived by reference methods, when it was first published it was the most accurate measure of GFR routinely available.[11]

Limitations to the MDRD include a negative bias at values higher than 60 mL/min/1.73m^2 (correctly written as mL.min^{-1}.1.73m^{-2}), a wide scatter with results not infrequently more than 30% from the reference value, a dependence on choice of creatinine measurement and invalidity in patients with rapidly changing renal function. As indicated above, many of these limitations apply to any creatinine-based method for estimating GFR. Also there is a described racial difference between black and white Americans which has raised the issue of possible differences in other racial groups. However, one key perceived benefit of the MDRD equation is in routine reporting, where it can provide an indication of reduced GFR without the need for further calculations.

More recently a formula has been developed based on over 8000 subjects from many centres covering a much wider range of patients.[16] This formula, known as the CKD-EPI equation, shows particularly improved performance compared to the MDRD formula at estimates higher than 60 mL/min/1.73m^2. A small local validation has confirmed this improved performance of CKD-EPI over the MDRD or C&G formulae.[17]

The Effect of Normalisation of Body Surface Area on eGFR

A key difference between the eCrCl and the eGFR are the units used to report the results. The C&G and measured creatinine clearance report results in mL/min, i.e. the actual volume of fluid passing through the glomeruli per unit time (the 'raw' GFR). By contrast the MDRD and CKD-EPI formulae report in mL/min/1.73m^2. This latter method of reporting is a normalisation based on the patient's body surface area (BSA). The principle is that a large person will generally have bigger kidneys and a higher raw GFR (in mL/min) than a smaller person of the same state of renal health. This is illustrated in Figure 2A where the effect of body size is removed by normalisation. In this calculation, subjects with BSA greater than 1.73 m^2 will decrease their result when normalised and subject with a BSA below this figure will increase their 'raw' GFR. Note that the BSA normalisation is built into the MDRD and CKD-EPI equations and thus the results are reported in mL/min/1.73m^2 without further calculation. It could be viewed that the serum creatinine itself already includes a balance between the muscle mass and the GFR of the patient, both of which are dependent on patient size, and thus already reflects these factors.

This difference in reporting format is potentially a significant issue when using an estimate of GFR for drug dosing decisions. A renally cleared drug is removed from the body proportional to the raw GFR rather than the normalised version. Thus the use of a normalised GFR will underestimate the drug removal in large people and overestimate in smaller people. This issue has been of particular concern to clinical pharmacologists.

A landmark paper in this field was Stevens *et al.* in 2009.[14] Using a data set with over 5000 subjects with formal measurements of GFR and the C&G and MDRD equations, it was shown that for 15 drugs with FDA guidance for dose adjustment by kidney function, MDRD correctly identified the dose reduction identified by formal GFR measurement 78% of the time and C&G was correct 73% of the time. A small note in this paper, which was easily missed on a quick reading, stated that 'we adjusted the BSA-adjusted values by multiplying by each individual's BSA and dividing by 1.73 m^2 so that all were expressed in units of milliliters per minute'. Thus the BSA normalisation was reversed prior to the analysis.

This raises the question as to whether there is data evaluating the MDRD (or CKD-EPI) equation when the BSA normalisation is removed. It is however readily apparent

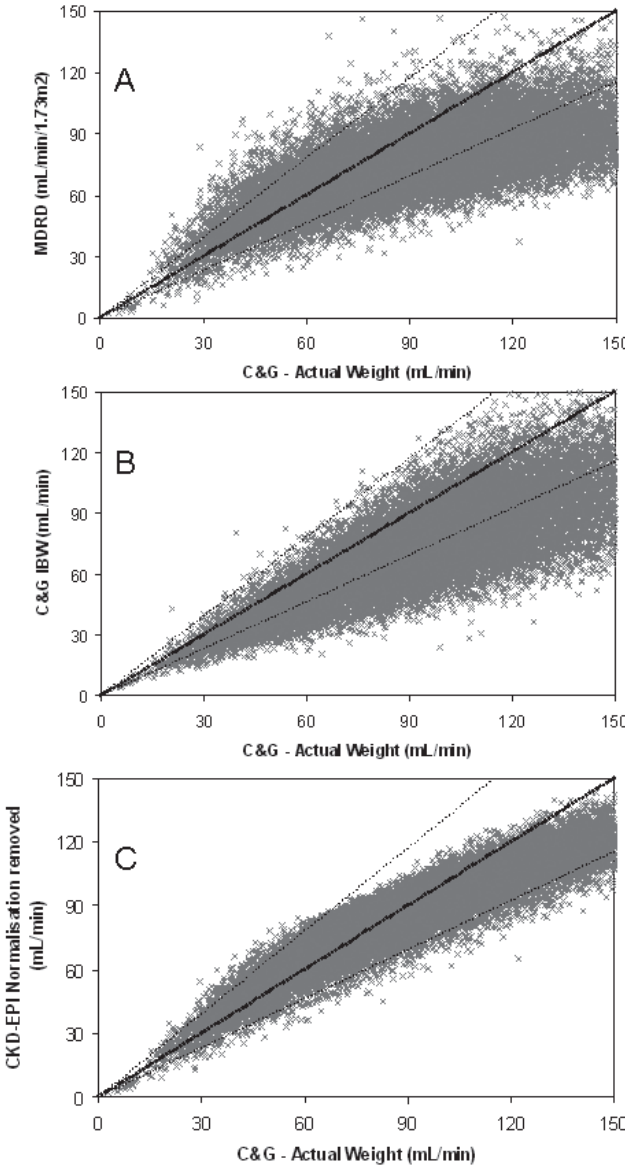

Figure 1. Comparison of (A) MDRD values for eGFR (B), Cockcroft and Gault eGFR calculated using patient ideal body weight and (C) CKD-EPI with body surface area normalisation removed with Cockcroft and Gault eCrCl using actual body weight. Data is from 32,000 Australians presenting for routine measurement of serum creatinine (9). The solid line is the line of identity and the dashed lines indicate differences of +/- 30%.

that the percentage differences between eGFR and measured GFR described in the evaluation studies are unchanged by the normalisation process. For any data point comparing MDRD (or CKD-EPI) with a measured GFR, the formal GFR result has been normalised. If that normalisation is removed from the eGFR and the formal GFR (dividing or multiplying both values by the same amount) the percentage difference is unchanged. Thus the published percentage accuracy data remains valid for results with the normalisation removed.

In order to remove the BSA normalisation it is necessary to calculate the BSA and then multiply the MDRD or CKD-EPI equation by the BSA/1.73. Ideally the Dubois and Dubois formula[18] should be used as this was the one used to develop the MDRD and CKD EPI formulae. Stevens used the Mosteller equation[19] for the drug dosing paper cited above, with the claim that this modification of the Gehan formula[20] was suitable for bedside use. In 2010 an equation for directly removing BSA normalisation with no greater complexity than the C&G formula was developed with an accuracy within +/- 10% of other more complicated formulae.[21]

The need to perform the removal of BSA normalisation depends on the clinical situation. As weight is the dominant contributor to BSA formulae, a simple rule can be based on the subject's weight. For patient's weight over about 70 kg the removal of normalisation will increase the GFR and for patients less than 70 kg the process will reduce the GFR. Thus in a 70 year-old woman with an eGFR of 55 mL/min/1.73m^2 and a weight of 50 kg, removal of the BSA normalisation will be necessary to assess changes in dose for a drug with a decision point at 50 mL/min. By contrast a 90 kg man with the same result will not require result adjustment as the GFR will increase with the removal of the BSA normalisation. This effect is shown in Figure 2B.

Recommendation

Based on the above discussion, I believe that the most appropriate formula for GFR estimation for drug dosing decisions is CKD-EPI formula, as this provides the most accurate estimate of GFR, with removal of BSA normalisation if needed. This has several advantages over the current situation. There is a clear numerical relationship between raw and BSA normalised eGFR; there are results which are valid for the standardised creatinine assays; and the eGFR results are directly traceable to formal GFR measurements. The use of a single formula with variations based on BSA normalisation also removes the need to explain the current use of different formulae for different indications (e.g. drug dosing or CKD classification). It is also of note that the results from the CKD-EPI equation with BSA normalisation removed correlate more closely with C&G than do other formulae (Figure 1C).

In practice, the C&G formula has a number of key supporting factors. At this time it is officially recommended for use, providing a defensible choice of formula. There is also very considerable experience with the formula, even if much of it is based on creatinine assays which are no longer in use. Given the limited need for great accuracy in the formulae and

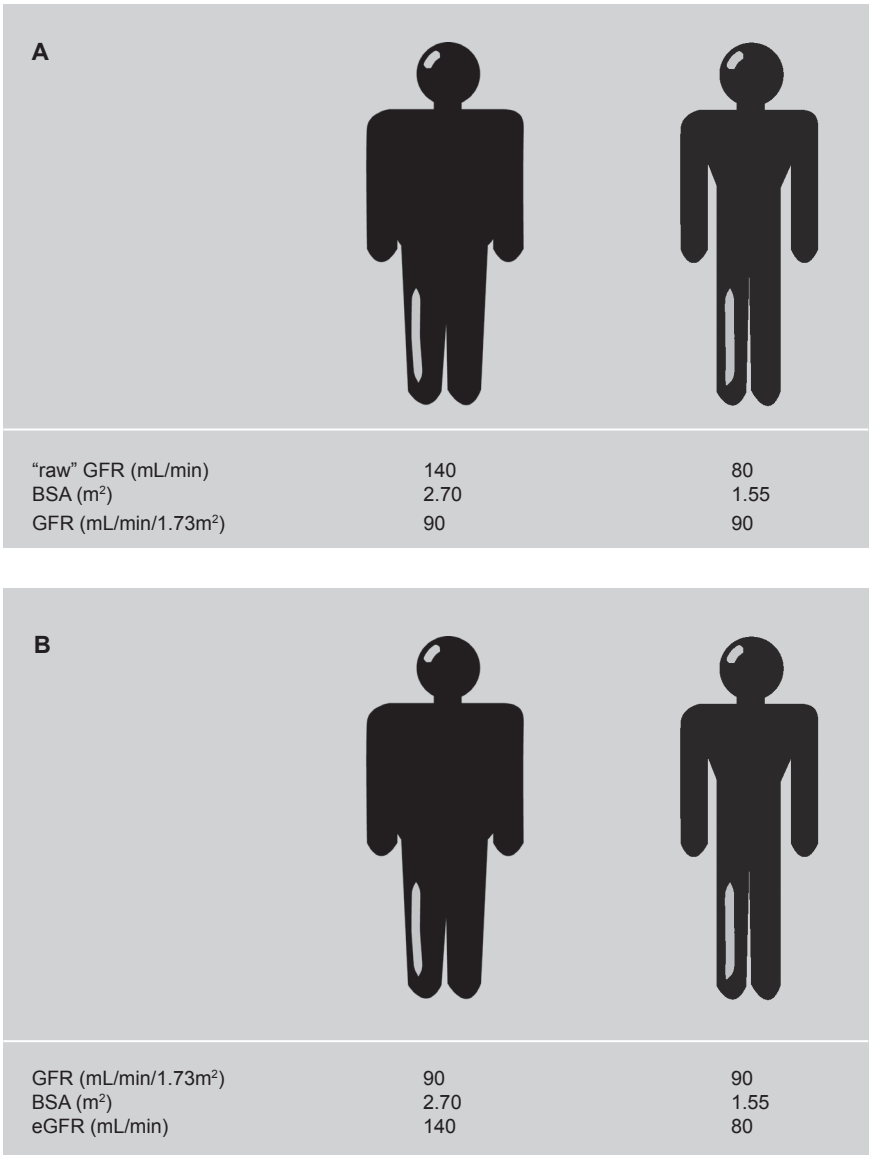

Figure 2. Schematic diagram showing the effects of (A) applying and (B) removing body surface area normalisation in subjects with very different body sizes.

the slow process of change in medicine, the approach taken by the NKDEP in the USA seems suitable: that either an eCrCl or an eGFR with BSA normalisation removed are acceptable.[22]

Competing Interests: None declared.

References

1. Doogue MP, Polasek TM. Drug Dosing in Renal Disease. Clin Biochem Rev 2011;32:69-73.
2. MIMS online. http://mims.hcn.net.au (Accessed 12 August 2010).
3. Therapeutic Guidelines. http://etg.hcn.net.au (Accessed 12 August 2010).
4. Australian Medicines Handbook. http://amh.hcn.net.au (Accessed 12 August 2010).
5. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16:31-41.
6. Mathew TH, Johnson DW, Jones GR. Chronic kidney disease and automatic reporting of estimated glomerular filtration rate: revised recommendations. Med J Aust 2007;187:459-63.
7. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med 1999;130:461-70.
8. Martin JH, Fay MF, Ungerer JP. eGFR – use beyond the evidence. Med J Aust 2009;190:197-9.
9. Gill J, Malyuk R, Djurdjev O, Levin A. Use of GFR equations to adjust drug doses in an elderly multi-ethnic

group – a cautionary tale. Nephrol Dial Transplant 2007;22:2894-9.
10. McBride G, Jones GR. Differences between GFR estimates using Cockcroft and Gault and MDRD equations: implications for drug dosing. Clin Biochem Rev 2005;26(Suppl):S42.
11. KDOQI Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification, and Stratification. http://www.kidney.org/professionals/KDOQI/guidelines_ckd/p5_lab_g4.htm (Accessed 30 September 2010)12. Myers GL, Miller WG, Coresh J, Fleming J, Greenberg N, Greene T, et al. Recommendations for improving serum creatinine measurement: a report from the Laboratory Working Group of the National Kidney Disease Education Program. Clin Chem 2006;52:5-18.
13. Jones GR, Imam SK. Validation of the revised MDRD formula and the original Cockcroft and Gault formula for estimation of the glomerular filtration rate using Australian data. Pathology 2009;41:379-82.
14. Stevens LA, Nolin TD, Richardson MM, Feldman HI, Lewis JB, Rodby R, et al. Comparison of drug dosing recommendations based on measured GFR and kidney function estimating equations. Am J Kidney Dis 2009;54:33-42.
15. Coresh J, Auguste P. Reliability of GFR formulas based on serum creatinine, with special reference to the MDRD Study equation. Scand J Clin Lab Invest Suppl 2008;241:30-8.
16. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150:604-12.
17. Jones GR. Use of the CKD-EPI equation for estimation of GFR in an Australian cohort. Pathology 2010;42:487-8.
18. DuBois D, DuBois EF. A formula to estimate the approximate surface area if height and weight be known. Arch Intern Med 1916;17:863-71.
19. Mosteller RD. Simplified calculation of body surface area. N Engl J Med 1987;317:1098.
20. Gehan EA, George SL. Estimation of human body surface area from height and weight. Cancer Chemother Rep 1970;54:225-35.
21. Jones GR. Estimated GFR for drug dosing: a bedside formula. Am J Kidney Dis 2009;54:982-3. (and Erratum. Am J Kidney Dis 2010;55:203)
22. CKD and Drug Dosing: Information for Providers. http://www.nkdep.nih.gov/professionals/drug-dosing-information.htm (Accessed 30 September 2010).

Appendix. Formulae used in Renal Assessment and Drug Dosing
Compiled by Graham Jones

Units for all formulae
Serum creatinine concentration (S Creat) in µmol/L; Weight (Wt) in kg; Height (Ht) in cm; Age in years

---

Estimated Creatinine Clearance (eCrCl)
Cockcroft and Gault formula[1]:
eCrCl (mL/min) = [(140 – Age) x Wt] / (0.813 x S Creat) (x 0.85 if female)

Estimated Glomerular Filtration Rate (eGFR)
MDRD formula with IDMS-aligned creatinine assays[2]:
eGFR-MDRD(mL/min/1.73m^2) = 175 x (S Creat × 0.0113)$^{-1.154}$ × age$^{-0.203}$ (× 0.742 if female)

CKD-EPI formula[3]:
Females, S Creat >62 µmol/L
eGFR-CKD-EPI (mL/min/1.73m^2) = 144 x (S Creat × 0.0113/0.7)$^{-1.209}$ × 0.993^{age}
Females, S Creat ≤62 µmol/L
eGFR-CKD-EPI (mL/min/1.73m^2) = 144 x (S Creat x 0.0113/0.7)$^{-0.329}$ x 0.993^{age}

Males, S Creat >80 µmol/L
eGFR-CKD-EPI (mL/min/1.73m^2) =141 × (S Creat x 0.0113/0.9)$^{-1.209}$ × 0.993^{age}
Males, S Creat ≤80 µmol/L
eGFR-CKD-EPI (mL/min/1.73m^2) =141 × (S Creat x 0.0113/0.9)$^{-0.411}$ × 0.993^{age}

Body Surface Area (BSA)
DuBois and DuBois formula[4]:
BSA (m^2) = 0.007184 × Ht$^{0.725}$ × Wt$^{0.425}$

Mosteller formula[5]:
BSA (m^2) = √(Ht × Wt / 3600)

Gehan and George formula[6]:
BSA (m^2) = 0.0235 x Ht$^{0.42246}$ × Wt$^{0.51456}$

Body Surface Area Normalisation (and Removal)
BSA normalisation:
GFR (mL/min/1.73m^2) = GFR (mL/min) × 1.73 / BSA

Removal of BSA normalisation:
GFR (mL/min) = GFR (mL/min/1.73m^2) × BSA / 1.73

Direct removal of BSA normalisation (Jones[7])
eGFR mL/min = eGFR (mL/min/1.73m^2) × (Wt x 6 + 600) / 1,000

Ideal Body Weight
Approximated from Devine formula[8]:
Ideal Body Wt = 50 + 0.9 x (Ht - 152) (-4.5 if female)

References

1. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16: 31-41.
2. Mathew TH, Johnson DW, Jones GR. Chronic kidney disease and automatic reporting of estimated glomerular filtration rate: revised recommendations. Med J Aust 2007;187:459-63.
3. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150: 604-12.
4. DuBois D, DuBois EF. A formula to estimate the approximate surface area if height and weight be known. Arch Int Med 1916;17:863-71.
5. Mosteller RD. Simplified calculation of body-surface area. N Engl J Med 1987;317:1098.
6. Gehan EA, George SL. Estimation of human body surface area from height and weight. Cancer Chemother Rep 1970;54:225-35.
7. Jones GR. Estimated GFR for drug dosing: a bedside formula. Am J Kidney Dis 2009;54:982-3. (and correction Am J Kidney Dis 2010;55:203).
8. Adult Ideal Body Weight Calculator. Australian Medicines Handbook. http://ww.amh.net.au/online/misc /idealweightcalculator.html (Accessed 19 April 2011).