Measuring glomerular filtration rate using chromium-51 EDTA: body surface area normalization before or after Brøchner-Mortensen correction?

Nuclear Medicine Communications 2015, 36:295–300 (Letters to the Editor)

Glen M. Blake, Mark C. Barnfield, Maria T. Burniston, Philip S. Cosgriff, John S. Fleming and Anthony W. Murray

We read with interest the article by Pottel et al. [1] 'Measuring glomerular filtration rate using 51Cr-EDTA: body surface area normalization before or after Brøchner-Mortensen correction?'. The authors question the basis for the recommendation in the British Nuclear Medicine Society (BNMS) guidelines [2] that glomerular filtration rate (GFR) measurements using the slope-intercept (SI) method be corrected for body surface area (BSA) before applying the Brøchner-Mortensen (BM) correction for the missing area under the curve (AUC). They argue that in Bröchner-Mortensen's original paper describing the correction of SI-GFR measurements in adults [3] there is no mention of the BSA adjustment, and that his correction for the missing AUC was derived using data that were not corrected for BSA. Furthermore, in a group of 20 children and young adults aged 5–22 years with Duchenne muscular dystrophy (DMD), the authors report that when the BM correction was applied first they found close agreement between the corrected SI-GFR and the true GFR calculated by fitting a biexponential curve, but a deviation of 5.5% when the BSA correction was applied first.

As authors of the BNMS guidelines [2], we acknowledge that in his 1972 paper [3] Bröchner-Mortensen developed the AUC correction using GFR measurements that were not corrected for BSA. However, the first paper published on a topic is rarely the last word on the subject. The 1972 paper dealt with a group of 74 adults with renal disease in whom the variation in BSA was modest, and the significance of the order in which the two corrections were applied was not obvious at the time. When, subsequently, in 1974 Bröchner-Mortensen et al. [4] described the AUC correction in children aged 1–12 years, the effect of performing the corrections in the wrong order became obvious, and they were duly applied in the right order: namely, the BSA correction first followed by the AUC correction. As demonstrated by Pottel et al. [1] in table 1 of their paper, for BSA values typical of adults the order in which the two corrections are applied causes differences of less than 5%, and hence in adults the choice is immaterial. To avoid confusion and ensure consistency between children and adults, and to promote uniformity in practice at different centres [5], when the BNMS GFR guidelines [2] were drafted it seemed reasonable to us to recommend the same approach in all patients.

There are additional reasons for believing that applying the BSA correction first is the right approach. SI-GFR is calculated by multiplying the volume of distribution (VD) by the slope kT of the terminal exponential (SI-GFR=VD × kT) [2]. As kT itself may be used as a measure of renal function that is independent of body size [6], the BSA correction can be regarded as an approximate adjustment of VD for differences in body size. The question then arises whether the same BSA adjustment should also be applied to the correction for the missing AUC. This issue was examined by Fleming [7], and also by Jødal and Brøchner-Mortensen (JBM) [8]. On the basis of a mathematical analysis of the two-compartment model, Fleming [7] derived an improved equation for correcting SI-GFR measurements for the missing AUC:

$$\text{True GFR} = \text{SI-GFR} / (1+f \times \text{SI-GFR}).$$

Expanding this equation and truncating it at the quadratic term we obtain:

$$\text{True GFR} = \text{SI-GFR-f x SI-GFR}^2,$$

showing that the BM correction is an approximation to Eq. (1). In his theoretical analysis Fleming showed that the coefficient f can be approximated by 1/4kEVP, where kE is the rate constant for the flow of tracer between the plasma compartment and the extravascular space and VP is the plasma volume. From this relationship and Eq. (2) it follows that the application of BSA correction before BM adjustment amounts to an assumption that the BSA body size correction should be applied to both VP and VD.

In a later paper based on an independent analysis, JBM also found an inverse relationship between Fleming's coefficient f and VP [8]. However, on the basis of chromium-51 EDTA (51Cr-EDTA) plasma clearance data on 134 men, women and children, instead of the expected linear relationship between VP and BSA, they found a power-law relationship with an index of 1.34. On the basis of these findings, JBM derived two self-consistent AUC correction formulae based on Eq. (1), one between the BSA-corrected values of SI-GFR and true GFR:

$$\text{TrueGFR}_{BSA} = \text{SI-GFR}_{BSA} / 1+0.00185 \text{x} \text{BSA}^{-0.3} \text{ x SI-GFR}_{BSA),}$$

and the second between the uncorrected GFR values:

$$\text{TrueGFR} = \text{SI-GFR} / (1+0.0032 \text{x} \text{BSA}^{-1.3}$$

$$\text{x SI-GFR}).$$

These equations have several advantages over the conventional BM correction. They can be applied to both children and adults, and are more accurate in children with high GFR [9], such as reported by Pottel et al. [1] for patients with DMD. Their use makes the debate about the correct order of applying the BM and BSA corrections irrelevant, as they provide completely self-consistent results starting with either the BSA-corrected or the BSA-uncorrected SI-GFR value.

We turn now to the data presented by Pottel et al. [1] on 20 children and young adults with DMD. We tested their recommendation of performing the BM correction first in an independent data set for 142 children and adults aged 0.6–56 years who underwent GFR studies at St James' Hospital, Leeds. A full description of the data has been published elsewhere [9]. The Leeds study used 99mTc-DTPA as the GFR tracer instead of 51Cr-EDTA, but the BM correction for the two tracers has been shown to be the same [10]. The SI-GFR was derived from 2, 3 and 4 h data, and true GFR from the full plasma curve

[Fig. 1:

Scatter plots of estimated GFR derived from the slope-intercept GFR against the true GFR calculated from multiple blood samples taken between 5 and 240 min after injection. Data are taken from the Leeds study [9]. Top row: results for 61 children under 13 years of age. Bottom row: results for 81 older children and adults. Left hand column (a, d): estimated GFR calculated as described by Pottel et al. [1] with the adult Brøchner-Mortensen (BM) correction [3] applied first followed by the correction for body surface area (BSA); Middle column (b, e): estimated GFR calculated by applying the BSA correction first followed by the paediatric BM [4] for children under 13 years of age and the adult BM [3] for older children and adults. Right hand column (c, f): estimated GFR calculated using the Jødal and Brøchner-Mortensen correction [8]. Diagonal lines are the lines of identity. GFR, glomerular filtration rate.]

starting 5 min after injection. Patients were divided into two groups: children aged 12 and younger, consistent with Brøchner-Mortensen's paediatric study [4], and older children and adults. Scatter plots of estimated GFR against true GFR were drawn for both groups in three ways:

(1) By applying the adult BM correction [3] before BSA correction, as suggested by Pottel and colleagues (Fig. 1a and d);

(2) By applying the paediatric BM correction [4] after BSA correction for children under 13 years, and using the corresponding adult BM correction [3] for older children and adults (Fig. 1b and e);

(3) Using the JBM correction [8] (Fig. 1c and f).

For older children and adults all three approaches for estimating GFR agreed closely with true GFR (Fig. 1d–f). For younger children the JBM correction gave good agreement over the full range of GFR values (Fig. 1c). In contrast, the Pottel method systematically overestimated true GFR, with larger deviations at higher GFR (Fig. 1a), whereas the BM paediatric equation gave good agreement up to 125 ml/min/1.73 m2 but plateaued at higher GFRs above the range of values described in the original paper [4] (Fig. 1b).

We look now at the GFR data for the 20 patients with DMD presented by Pottel and colleagues. We used a web digitizer [11] to extract the BSA-corrected true and SI-GFR values from figure 2 of their paper [1] and evaluated Fleming's coefficient f by substitution in Eq. (1). We found a mean value (95% confidence interval) of 110 × 10−5 (84 × 10− 5–135 × 10− 5) (ml/min/1.73m2) − 1, compared with the 170 × 10− 5 (ml/min/1.73m2) – 1 reported by Fleming [7]. We substituted the mean BSA value of 1.33m2 reported by Pottel and colleagues for their group of 20 children and young adults in the JBM correction equation [8] and found a predicted mean value for the DMD patient group of f= 170 × 10− 5 (ml/min- /1.73m2)− 1. When we substituted the same BSA value in the Leeds equation [9] we found a predicted value of f= 184 × 10− 5 (ml/min/1.73m2) −1.

We conclude that the results published by Pottel and colleagues overestimated the true GFR in their DMD patients because they underestimated the missing AUC, as demonstrated by the low value of f derived from their study. It is possible that this overestimation of true GFR arose because in their protocol the first blood sample was not taken until 15 min after EDTA injection, compared with the usual time of 5min [4,8–10]. As shown by Pottel's analysis, in patients with BSA values less than 1.73m2, such as children, reversing the order of corrections by applying the BM correction first results in higher values of estimated GFR. It is clear that the conclusion of Pottel and colleagues regarding the order of application of the BM and BSA corrections amounts to compensating for the overestimation of true GFR caused by the underestimation of the missing AUC by inverting the order of the two corrections. For children with high GFR, such as in the DMD group, we believe that the most reliable method of adjusting SI-GFR is the JBM correction [8].

References

1 Pottel H, Hoste L, de Waele L, Braat E, Baete K, Goffin K, et al. Measuring glomerular filtration rate using 51Cr-EDTA: body surface area normalization before or after Bröchner-Mortensen correction? Nucl Med Commun 2014; 35:1150–1155.

2 Fleming JS, Zivanovic MA, Blake GM, Burniston M, Cosgriff PS, British Nuclear Medicine Society. Guidelines for the measurement of glomerular filtration rate using plasma sampling. Nucl Med Commun 2004; 25:759–769.

3 Bröchner-Mortensen J. A simple method for the determination of glomerular filtration rate. Scand J Clin Lab Invest 1972; 30:271–274.

4 Bröchner-Mortensen J, Haahr J, Christoffersen J. A simple method for accurate assessment of the glomerular filtration rate in children. Scand J Clin Lab Invest 1974; 33:140–143.

5 Murray AW, Lawson RS, Cade SC, Hall DO, Kenny B, O'Shaughnessy E, et al. UK audit of glomerular filtration rate measurement from plasma sampling in 2013. Nucl Med Commun 2014; 35:1096–1106.

6 Peters AM, Glass DM, Bird NJ. Extracellular fluid volume and glomerular filtration rate: their relation and variabilities in patients with renal disease and healthy individuals. Nucl Med Commun 2011; 32:649–653.

7 Fleming JS. An improved equation for correcting slope-intercept measurements of glomerular filtration rate for the single exponential approximation. Nucl Med Commun 2007; 28:315–320.

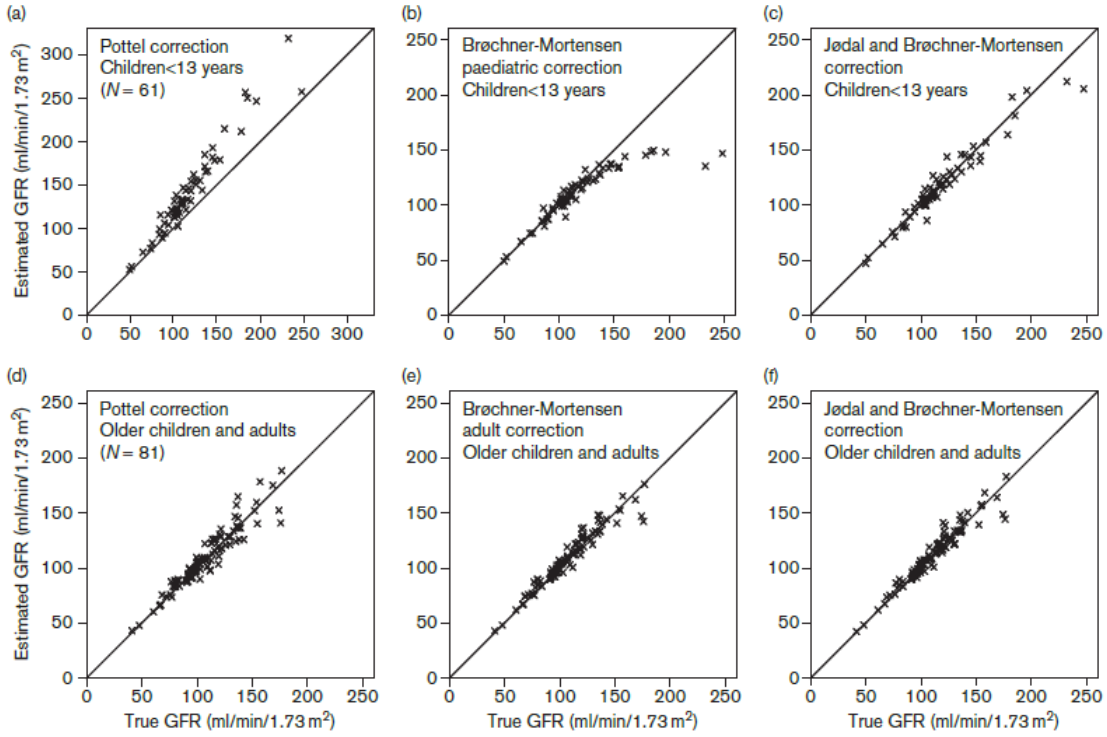
8 Jødal L, Brøchner-Mortensen J. Reassessment of a classical single injection 51Cr-EDTA clearance method for determination of renal function in children and adults. Part I: analytically correct relationship between total and one-pool clearance. Scand J Clin Lab Invest 2009; 69:305–313.

9 Blake GM, Barnfield MC, Burniston MT, Fleming JS, Cosgriff PS, Siddique M. Correction of the slope-intercept method for the measurement of glomerular filtration rate. Nucl Med Commun 2014; 35:1277–1283.

10 Fleming JS, Wilkinson J, Oliver RM, Ackery DM, Blake GM, Waller DG. Comparison of radionuclide estimation of glomerular filtration rate using technetium 99m diethylenetriaminepentaacetic acid and chromium 51 ethylenediaminetetraacetic acid. Eur J Nucl Med 1991; 18:391–395.

11 Web Plot Digitizer. Web based tool to extract data from plots, images, and maps. Version 3.4 released September 22 2014. Available at: http://www.arohatgi.info/WebPlotDigitizer. [Accessed 31 October 2014].

Fig. 1


(a)
Pottel correction
Children<13 years
(N = 61)
(b)
Brøchner-Mortensen
paediatric correction
Children<13 years
(c)
Jødal and Brøchner-Mortensen
correction
Children<13 years
(d)
Pottel correction
Older children and adults
(N = 81)
(e)
Brøchner-Mortensen
adult correction
Older children and adults
(f)
Jødal and Brøchner-Mortensen
correction
Older children and adults
Estimated GFR (ml/min/1.73 m²)
True GFR (ml/min/1.73 m²)