Indexed glomerular filtration rate as a function of age and body size

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ABSTRACT

The conventional way in which to scale or index a measurement of glomerular filtration rate (GFR) is to express it in relation to body surface area (BSA). However, BSA may not be appropriate for infants and children because, as individuals increase in size, their relative BSA decreases. Several other whole-body variables have been suggested as alternatives, including extracellular fluid volume (vECF). The purpose of the present study was to compare BSA and vECF as variables against which to index GFR, and in particular to look at this comparison in children versus adults. A total of 130 patients (age range 1–80 years; 40 patients < 12 years) undergoing clinically indicated routine measurement of GFR using the bolus-injection single-compartment technique were included in the study. GFR was measured as the plasma clearance of $[^{51}\text{Cr}]$EDTA as assessed from three peripheral venous blood samples taken between 2 and 4 h after injection of $[^{51}\text{Cr}]$EDTA. Volume of distribution ($V_d$) was obtained by extrapolation of the clearance curve to zero time. GFR was scaled to a BSA of 1.73 m$^2$. GFR and GFR/1.73 m$^2$ were corrected to account for the assumption of a single compartment. The rate constant of the exponential between 2 and 4 h was also corrected to give GFR/litre ECF. GFR and GFR/1.73 m$^2$ were both divided by GFR/litre ECF, to give vECF and vECF/1.73 m$^2$ respectively. Weight per unit BSA increases as a linear function of BSA. vECF is always less than $V_d$, on average by about 30%. vECF increased as an exponential function of BSA and as a linear function of body weight. vECF/70 kg body weight was higher in children (16.2 ± 3 litres) than adults (13.4 ± 2.3 litres), but vECF/1.73 m$^2$ was lower in children (9.7 ± 1.7 litres) compared with adults (12.4 ± 2 litres). vECF/1.73 m$^2$ increased as a function of both age and BSA, but vECF/kg decreased. GFR/12.5 litres vECF was higher than GFR/1.73 m$^2$ in children, but these values were similar in adults, with the ratio of these two forms of indexed GFR falling significantly with both age and BSA. Although this was not a normal population, but one with a wide range of renal function, GFR/vECF showed a strong inverse association with age, whereas for GFR/BSA the association was weak. In conclusion, these data provide further evidence that vECF is more valid physiologically for indexing GFR than is BSA, especially in children. Nevertheless, a GFR measurement in a child should ideally be expressed as a percentage of normal for that child’s age. However, such normal values are not yet available.

Key words: $[^{51}\text{Cr}]$EDTA, extracellular fluid volume, glomerular filtration rate, renal function.

Abbreviations: BSA, body surface area; ECF, extracellular fluid; GFR, glomerular filtration rate; $V_d$, volume of distribution; vECF, extracellular fluid volume.

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INTRODUCTION

In order to compare renal function between individuals of widely ranging size and to be able to define a single normal value, glomerular filtration rate (GFR) is conventionally indexed to body surface area (BSA). Several alternative whole-body parameters are, however, available against which to index GFR, including body weight [1–3], lean body mass [4,5], total body water [6], plasma volume [7] and extracellular fluid (ECF) volume (vECF) [1,8–12]. There is little to choose between these whole-body variables as far as adults are concerned, but for children indexing is more critical, and several arguments have been put forward against BSA [5,6,9].

The gold-standard for GFR is urinary inulin clearance, but this is seldom performed in routine clinical practice because it is difficult and cumbersome. Instead, GFR is now almost universally measured using the bolus-injection single-compartment technique, which measures the plasma clearance of a substance which is not protein-bound in plasma, not reabsorbed by the renal tubular epithelium and shows no extrarenal clearance. While inulin satisfies these criteria best, and can be used with this technique [9,12], it has largely been replaced by the radioactive filtered compounds [51Cr]EDTA and [99mTc]diethylenetriaminepenta-acetic acid (DTPA).

Indexing GFR against vECF has the attraction that the rate constant z2 of the terminal exponential of the plasma clearance curve is a measure of GFR which is already normalized for vECF [9,11,12]. Furthermore, GFR/vECF may be a physiologically more appropriate measurement of renal function than GFR/1.73 m², especially in children [1]. Although it is not completely clear at what age GFR/1.73 m² is considered to reach adult values, GFR/vECF may be higher than adult values from as young as 6 months [1]. The purpose of the present study was to further compare GFR/vECF with GFR/BSA and, in particular, to look at how these parameters change during growth and maturation in order to determine the extent to which they are interchangeable in children and adults.

METHODS

Data were analysed from 143 consecutive GFR measurements made with [51Cr]EDTA in patients (aged 1–80 years) routinely referred as part of their clinical management to the Nuclear Medicine Department with a wide range of clinical indications, including management of a nephro-urological disorder and in relation to cancer chemotherapy. The bolus-injection single-compartment technique was used. In this technique, it is assumed that mixing of tracer throughout its volume of distribution (Vd; the single compartment) is instantaneous. In fact mixing takes up to 2 h, producing a multiexponential plasma clearance curve which reduces to a single exponential, with rate constant z2, within 2 h of tracer injection. Antecubital venous blood samples were therefore obtained 2, 3 and 4 h after intravenous injection of 3 MBq/kg body weight of [51Cr]EDTA (Mallinkrodt). 51Cr counts in each sample were compared with those in a standard. The height and weight of each patient was measured, and BSA was calculated using a standard conversion table.

Data analysis

Plasma [51Cr]EDTA clearance was expressed logarithmically and a least-squares fit applied to the three data points of each curve to generate the rate constant z2 (min⁻¹) of the terminal exponential. GFR and Vd were calculated from the standard equations:

\[ V_d = \frac{\text{administered radioactivity}}{\text{zero-time intercept of terminal exponential}} \]

and

\[ \text{GFR} = V_d \times z_2 \]

The correlation coefficient of the least-squares fit to the three data points was considered unsatisfactory when it was less than 0.99; 11 studies were therefore considered unreliable on these grounds and eliminated. Only two plasma samples were available in a further patient, whose results were therefore also eliminated. This left 131 GFR measurements. GFR (ml/min) and Vd (ml) were normalized (i.e. scaled or indexed) to a BSA of 1.73 m². GFR/1.73 m² was then corrected to account for the overestimation which results from the assumption of a single compartment. A previously published formula, based on a second-order polynomial fit to a large group of patients receiving [51Cr]EDTA in whom the one-compartment model had been compared with the more accurate two-compartment model, was used to make this correction [13].

As described in an earlier theoretical treatment [11], the rate constant of the exponential, z2, fitted to the three data points is a close approximation to GFR per unit Vd. Because the Vd of [51Cr]EDTA represents vECF, z2 is also a close approximation to GFR/litre ECF, systematically slightly underestimating it. z2 was therefore also corrected to give GFR/litre ECF using a previously described formula [11]. Note that GFR/vECF is already normalized for body size. GFR/1.73 m² was divided by GFR/litre ECF to give GFR/1.73 m². For one patient (aged 3 years), the last-mentioned value was 5 S.D.s above the mean for children up to age 12 years (see below). This child’s GFR was measured as 213 ml·min⁻¹·1.73 m² BSA and as 136 ml·min⁻¹·12.5
litres\(^{-1}\) ECF. The value indexed to BSA was considered erroneous, and the patient was eliminated from the study, leaving a total of 130 patients, of whom 40 were less than 12 years old (see below). Absolute vECF was obtained by dividing GFR (which had been corrected but not indexed to BSA) by GFR/litre ECF. For comparison with GFR/1.73 m\(^2\), GFR/litre ECF was multiplied by 12.5 litres, a volume taken to be the vECF of a standard human, i.e. 12.5 litres/1.73 m\(^2\).

### RESULTS

As individuals increase in age, body weight per unit BSA increases up to about age 12 years at a rate of approx. 7% per year (Figure 1a). At about age 12 years, this rate of increase slows down abruptly, but the ratio continues to increase slowly at a rate of about 0.7% per year. For comparison of children with adults, therefore, we chose 12 years as the cut-off age. As individuals increase in size, body weight per unit BSA increases as a linear function of BSA, with children and adults showing very similar regressions (Figure 1b). vECF is always less than V\(_d\) by about 30%, although the regressions of vECF on V\(_d\) were significantly different between children and adults (Figure 2). vECF increases as an exponential function of BSA (Figure 3a), but as a linear function of body weight (Figure 3b). The relationship between indexed vECF and BSA depends on the variable against which vECF is indexed. Thus vECF/1.73 m\(^2\) increases whereas vECF/70 kg decreases (Figure 4), such that whereas the choice of index makes no difference in adults, vECF/70 kg was significantly higher than vECF/1.73 m\(^2\) in children (P < 0.001). In adults vECF/70 kg was 13.4 (S.D. 2.3) litres compared with 16.2 (3) litres in children (P < 0.001), while vECF/1.73 m\(^2\) was 12.4 (2) litres in adults compared with 9.7 (1.7) litres in children (P < 0.001).

In children, GFR/12.5 litres vECF was generally higher than GFR/1.73 m\(^2\), but these values were similar in adults (Figure 5). The ratio of GFR/12.5 litres vECF to...
Figure 3  Relationships between vECF and (a) BSA and (b) body weight
vECF increases as an exponential function of BSA and as a linear function of body weight.

Figure 4  vECF indexed to 1.73 m$^2$ BSA (•) or 70 kg body weight (○) as a function of BSA in children and adults combined

Figure 5  Ratio of GFR/12.5 litres vECF to GFR/1.73 m$^2$ BSA as a function of BSA
The data have been fitted with an exponential function.

GFR/1.73 m$^2$ decreased significantly as a function of BSA (Figure 5). BSA and age are correlated (Figure 1), so it was not surprising that this ratio also decreased significantly with age (results not shown). Using 90 ml/min as the cut-off for a normal indexed GFR, 68/90 (76%) adults were abnormal based on GFR/1.73 m$^2$, and 71/90 (79%) were abnormal based on GFR/12.5 litres. In contrast, 28/40 children (70%) had abnormal function based on GFR/1.73 m$^2$, but only 13/40 (33%) were abnormal based on GFR/12.5 litres. Notwithstanding that this is an abnormal population, GFR/12.5 litres showed a significant inverse association with age. GFR/1.73 m$^2$, in contrast, showed a weak association with age (Figure 6).
DISCUSSION

These results in general, and the differences between children and adults in particular, can be traced to the fact that small individuals have a higher BSA in relation to body weight. However, the implications from this simple fact for how we index GFR are substantial. Received wisdom is that filtration function does not reach full maturity until about age 5 years [14], or even later [15], when GFR/BSA approaches normal adult values. However, when expressed in relation to body fluid volumes, GFR reaches maturity, or at least adult normal values, very much earlier (~6 months), and soon exceeds adult values thereafter [1].

In concert with hormonal control and tubular function, the purpose of glomerular filtration is to regulate body fluid composition, and, although it is plasma that is filtered, this ultimately includes interstitial and intracellular fluids. *A priori*, therefore, perhaps the most rational whole-body variable against which to normalize GFR would appear to be total body water, and strong arguments supporting this were put forward long ago [6]. Plasma volume, vECF and lean body mass are all closely linked to total body water and are potential alternatives for normalization.

The attraction of plasma volume, and especially vECF, is that indexed values of GFR, as quotients of these two volumes, can be generated directly, and this is technically easier than separate measurements of the numerator and denominators of the quotients. Thus GFR/vECF is a close approximation to $a_\lambda$, the terminal exponential of the plasma clearance curve following bolus injection. GFR/litre ECF has the further advantage that it can be measured in real time by external monitoring of tissue radioactivity with a miniaturized probe [16], an application for which it has recently been validated [17]. A disadvantage is the requirement of an $a_\lambda$ value with a high statistical confidence. A poor fit to the terminal exponential when measuring absolute GFR, on the other hand, and any resulting error in $a_\lambda$, tends to be counterbalanced by an opposing error in $V_d$ [13]. Nevertheless, the correlation coefficient for the fit to the three data points was less than 0.99 in only 11/142 studies and less than 0.98 in only one. Increasing the number of samples to four improves statistical confidence. It should be realized that, when $a_\lambda$ is decreased, the correlation coefficient also tends to be lower, so a value of less than 0.99 may be acceptable in a patient with poor filtration function. When using a scintillation probe to record $a_\lambda$, there are many data points, and statistical significance ceases to be an important issue.

In contrast with vECF/BSA, vECF/body weight is significantly higher in children than in adults. This, however, may be partly explained by greater obesity in adults. A whole-body variable which would be eminently suitable for normalizing both GFR and vECF, and which is becoming increasingly possible to measure with whole-body densitometry, is lean body mass.

A comparison of the respective changes in GFR/BSA and GFR/vECF as infants mature into adults would be an important study, but difficult to perform because of ethical limitations. Only a hazy view of such a comparison can be obtained from a patient population with widely ranging levels of renal function such as this one. Nevertheless, it can be clearly seen that GFR/vECF declined with age, whereas GFR/BSA showed no significant association with age. As vECF, if anything, also decreases with age [18], this hints strongly that GFR also decreases with age, but that indexing to BSA fails to detect the decrease.

If GFR/litre ECF is higher in children than in adults, if vECF is also relatively higher in early childhood, and if turnover of ECF is a physiologically more appropriate
way to assess glomerular filtration than expressing GFR in terms of BSA (all probably true), then one can confidently assert that filtration function matures at an early age, certainly by 2 years. GFR/litre ECF is the reciprocal of the mean time that a molecule of tracer waits in the ECF before filtration. Transit, residence and waiting times in relation to several physiological systems, especially the circulatory system, are shorter the smaller the organism (e.g. mean circulation time). Therefore the high values for GFR/litre ECF in infancy and childhood could be perceived as unremarkable, and simply as another example of this general rule. In this case, there would be a unique normal value for GFR for every age during childhood. This would imply that the preferred method of expressing GFR in children would be as a percentage of normal for that age or body size (preferably lean body mass). The difference between children and adults with respect to the regression of vECF on V, also implies that correction factors for absolute GFR and a (as a measure of GFR/vECF) need to be tailored for children.

We conclude that, in children, BSA is a questionable whole-body variable against which to index GFR, and that for technical and physiological reasons GFR indexed to vECF is to be preferred. A normal value of GFR/litre ECF should be established for all ages or body sizes during childhood.

REFERENCES


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