

Glomerular filtration rate—what is the rationale and justification of normalizing GFR for body surface area?

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are used to estimate BSA and alternative ways of indexing GFR.

Introduction

We were presented with a 54-year-old man who wished to donate a kidney to his 21-year-old son who had established renal failure. Live donor work up of the father was satisfactory except for borderline kidney function; glomerular filtration rate (GFR) measured by plasma clearance of ⁵¹Cr[EDTA] was 87.0 ml/min uncorrected for body surface area (BSA) and 77.9 ml/min/1.73 m². Should kidney donation proceed? Published international guidelines [1] and UK guidelines [2] recommend a minimum GFR of 80 ml/min/1.73 m² and 75 ml/min/1.73 m² respectively for a 55-year-old prospective kidney donor. The 9.1 ml/min difference between the absolute GFR and the GFR indexed for BSA prompted further consideration of the validity and rationale for indexing GFR to BSA.

There are several formulae that estimate BSA from measures of height and weight in the literature and in this man, with height 1.65 m and weight 86 kg, we found that the application of six previously published height–weight formulae to estimate BSA [3–8] gave a range of indexed GFR of 72.0 to 77.9 ml/min/1.73 m². In other words, indexing GFR for BSA in this man reduced the value for GFR by between 9.1 and 15 ml/min depending on which BSA formula was used and greatly influenced the decision about his suitability as a kidney donor.

Several authors have questioned the validity of indexing GFR for BSA and the generalizability of the supporting studies from the last century to the increasingly obese population [9–12]. The purpose of this review is to explore the physiological plausibility of using BSA as an appropriate way to index measured GFR, the validity of the methods that

Is body surface area the appropriate index for GFR?

Since the basic function of the kidneys is to clear the waste produced by the body, it is intuitively necessary to index GFR for a measure of body size to be able to compare values of GFR between individuals. In the nineteenth century it became widely accepted that, regardless of species, the metabolic rate of an animal is closely related to BSA [13] although the evidence to support this hypothesis in humans was sparse. As a result it became commonplace to index physiological variables to BSA. As far back as 1928 McIntosh *et al.* proposed indexing kidney function to BSA in one of the early papers describing the concept of renal clearance [14]. They proposed 1.73 m² as the index value as this was found to be the average calculated BSA of 25-year-old Americans of that time. The fact that the BSA calculated from height–weight formulae of adults in most countries has increased since then (because of increasing body weight) does not invalidate indexing of GFR by BSA because the index value is arbitrarily chosen. They could, for example, have chosen 1 m² as the index value. Indeed it is important that the index value stays constant to facilitate studies that use historical comparisons.

The best way to test the ‘clinical’ validity of indexing GFR to a measure of body size is to determine the impact of this on clinically important outcomes. We are not aware of any studies that have compared absolute GFR with GFR indexed for BSA (or any other measure of body size) in predicting outcomes such as rate of progression of chronic kidney disease or living donor kidney function. However, the physiological plausibility of indexing, at least to some measure of body size, is supported by observational studies; for example, in the field of transplantation outcome is better in female recipients of male donor kidneys compared to male recipients of female donor kidneys [15].

Since the purpose of glomerular filtration is to regulate body fluid composition it has long been argued that it is more logical to index GFR to a measure of fluid volume

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such as total body water [16] or extracellular fluid volume (ECFV) [17] than BSA. If GFR is measured using a plasma clearance method (using, for example, $^{51}\text{Cr}[\text{EDTA}]$, $^{99\text{m}}\text{Tc-DTPA}$ or iohexol) then ECFV can be derived from the relationship $\text{GFR}/\text{ECFV} = \alpha_2$ where α_2 is the rate constant (min^{-1}) of the terminal exponential of the plasma clearance curve [9]. Using this relationship Peters *et al.* were able to present a series of observations that expose the physiological implausibility of estimated BSA to index GFR for body size if it is accepted that ECFV is a sensible indexing variable [18]. For example, ECFV is three-dimensional whereas BSA is two-dimensional; GFR/ECFV shows a strong inverse correlation with age whereas the association is weak for GFR/BSA , and $\text{ECFV}/1.73 \text{ m}^2$ increases as a function of BSA.

Use of an index variable to normalize a physiological variable implies a linear relationship between the two with a zero intercept. The strength of this relationship for GFR and BSA is questionable with some studies showing a correlation coefficient as low as 0.24 [19].

Are estimates of BSA using height and weight valid?

Meeh published a formula to estimate BSA using body weight in 1879 that had been derived in 10 adults and 6 children by using tracing paper and calculating areas by geometry or weighing the paper [20]. This remained standard until 1915 when the Du Bois brothers published several manuscripts exploring different formulae to measure BSA. They measured true BSA using moulds of gummed manila paper applied to the body and then laid on photographic paper of known weight from which the unexposed pieces could be cut out and weighed [21]. They used detailed measures of different body parts to derive a formula to predict BSA that had an acceptably limited error compared with the true BSA. The calculations were sophisticated considering they had to be done by hand but only 11 individuals (including one child) with widely varying body habitus were used. The first formula required 19 measures from 7 body parts, so it was unsuitable for wide application. However, a 'height-weight' formula derived from the same dataset was felt to be sufficiently accurate to have merit and, in what has been described as a 'triumph of simplicity over accuracy' [22], this formula ($\text{BSA} [\text{m}^2] = 0.007184 \times \text{weight} [\text{kg}]^{0.425} \times \text{height} [\text{cm}]^{0.725}$) [3] has been widely applied ever since. Subsequent authors have demonstrated that the Du Bois equation tends to underestimate BSA in children [6] and overestimate BSA in obese subjects [8]. Refinements to the height-weight formula have been offered by using larger cohorts [4], re-analysing previous data [5], or including subjects that were under-represented in preceding publications (children, obese subjects and black subjects) [6,8,23]. These refinements serve to emphasize that it is unrealistic to expect a single height-weight formula to predict BSA with accuracy since humans change shape as they grow [24] and, for any given height and weight, there is obviously a wide range of body shape. It is obvious that any errors in height-weight formulae will be exaggerated

in obese subjects. This has important implications as the prevalence of obesity continues to rise.

Why does BSA continue to be used to index GFR in clinical practice?

Despite all of these concerns BSA continues to be used to index GFR. The four-variable MDRD formula that has gained widespread acceptance as the most appropriate measure of kidney function in routine clinical practice was derived by using serum creatinine, age, sex and race to predict $\text{GFR}/1.73 \text{ m}^2$ BSA [25]. This requires only a single blood sample and has emerged as a convenient way of estimating kidney function compared with other methods such as creatinine clearance (which requires a timed urine collection) or plasma clearance methods that require injection of a tracer and timed blood samples. We have to consider the possibility that the flaws described in indexing GFR to BSA introduce unacceptable inaccuracy to MDRD eGFR as a measure of kidney function. If that was true then there would be an argument for repeating the analysis of the MDRD study data to create a new serum creatinine based formula to predict GFR scaled to ECFV. However, the reality is that indexing for BSA tends to have little influence on routine clinical practice because, for most patients, measurement of GFR or estimation of GFR is done to detect changes in kidney function; the magnitude of the changes will be essentially the same whether the GFR is expressed as an absolute value or indexed for BSA (unless there has been a very large change in body weight). Furthermore, in normal sized adults, indexing for BSA adjusts the GFR by no more than a few ml/min and this usually has no important influence on clinical decisions. However, in situations where a single measure of GFR is used to guide clinical decisions (such as living kidney donor suitability), indexing for BSA can lead to a change in the clinical decision especially in children and the overweight.

Should ECFV be used to index GFR instead of BSA?

When contemplating a change to using ECFV to index GFR rather than BSA it is worth noting that a direct measure of ECFV is not required. This is because, as stated earlier, α_2 , the rate constant of the terminal exponential of the plasma clearance curve, is a direct measure of GFR/ECFV . Bird *et al.* derived a height-weight formula to predict ECFV in subjects who had meticulous measurement of absolute GFR and α_2 [24]. Using this equation the ECFV corresponding to a height-weight formula derived BSA of 1.73 m^2 is 12.9 l. Peters *et al.* used this equation to compare GFR indexed to 1.73 m^2 BSA with GFR indexed to 12.9 l ECFV in the same subjects and found that there was a close correlation in adults [9]. This suggests that for most adults indexing GFR for ECFV will achieve almost identical results to indexing for BSA, probably because of the close relationship between ECFV and BSA inherent in their relationship to

body weight. In children, however, GFR indexed according to BSA was about 20% lower.

What should be done?

The merit of abandoning the practice of indexing GFR (or eGFR) for BSA in favour of the more logical ECFV in routine adult clinical practice does not really justify the upheaval that this would involve. However, it should be appreciated that results of GFR indexed for BSA in obese patients may be a substantial underestimate of true kidney function and should be interpreted with caution. The validity of BSA to index GFR and the methods to estimate BSA are sufficiently insecure to mean that definite statements about acceptability for specific interventions in adults should perhaps be accompanied by a statement about the imprecision that is associated with the BSA calculation. In children there is a stronger argument for changing practice to indexing GFR for BSA as the tendency of BSA formulae to underestimate true BSA and the observation that $\text{GFR}/1.73 \text{ m}^2 \text{ BSA}$ tends to be approximately 20% lower than $\text{GFR}/12.9 \text{ l ECFV}$ means that indexing GFR for BSA could be a clinically important overestimate or underestimate of true kidney function in an individual child.

It should be possible to explore the clinical value of indexing GFR by re-analysing data from studies in which large cohorts of patients representing different demographic groups had measures of GFR. These could be used to determine which method of indexing GFR, if any, correlates better than absolute GFR with important clinical end-points such as rate of progression of kidney failure, incidence of future cardiovascular events and death, kidney transplant survival and living donor kidney function.

For most situations where a measure of kidney function is required, it is practical to accept the physiological flaws and sacrifice of accuracy for simplicity inherent in indexing GFR for BSA. However, as illustrated by the potential living kidney donor presented, the clinician must be alert to situations where these imperfections may be influencing clinical decisions.

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