

Errors induced by indexing glomerular filtration rate for body surface area: *reductio ad absurdum*

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Introduction

In this article, we will discuss an important but under-recognized topic in nephrology. Indeed, indexing glomerular filtration rate (GFR) for body surface area (BSA) is often done by habit, because everyone does it and without raising any questions. Only a scant literature on this topic has been published in recent decades. Regarding guidelines on estimating and measuring GFR, only the Australian ones deeply discuss this topic. However, indexing GFR is not free from criticisms and may be misleading, especially in some specific populations. As we have pointed out, indexing GFR for BSA has very limited consequences on GFR results in a 'normal' body size population, but its consequences are substantial in other populations such as obese or anorectic patients [1,2]. In this editorial, we would like to show the limitations of such an indexation and give some evidence of its inadequacy.

Indexing GFR for BSA: the genesis

The original article regarding indexation of GFR for BSA was published in 1928 by McIntosh [3]. This author was also the first to use the factor '1.73 m²' for that indexation, which is itself questionable, as it has been elegantly shown by Heaf [4]. McIntosh compared renal function, as urea clearance, in 18 adults and 8 children. Indexing GFR for BSA gave comparable urea clearance results between children and adults [3]. In other words, the values for GFR became less dispersed by the indexation. These data were confirmed in 1931 by Holten who studied 90 children and adolescents using creatinine clearance [5]. However, decreasing the dispersion of the data is not a strong argument for BSA indexing [6]. McIntosh had also built his indexation theory with experience from earlier American physiological studies [3]. In 1923, Taylor described an 'approximately'

direct correlation between urea excretion and the weight of the kidney in 23 rabbits [7]. Parenthetically, 'approximate' correlations would not pass muster today. This author also described a better correlation between kidney weight and BSA than between kidney weight and animal's weight. Such a conclusion had also been made by Stewart on a limited number of dogs [8]. We have re-calculated this correlation with data given by Taylor in his original article and noted that the correlation between BSA and kidney weight ($r = 0.94$) was not different from that between kidney weight and body weight ($r = 0.96$). In 1932, MacKay illustrated a direct correlation between BSA and kidney weight and between BSA and urea excretion in humans [9]. From these observations, McIntosh concluded that BSA was strongly correlated with renal function [3]. However, this conclusion may be viewed as too optimistic, as BSA had not been directly compared to GFR, but just to urea excretion. Holten described a correlation between creatinine clearance and BSA, but he thought that this relationship was not direct but linked to the common relation to basal metabolic rate (BMR). He based this hypothesis on studies showing that thyroidectomy decreased kidney weight on one hand and that giving thyroid hormones increased protein metabolism and kidney weight on the other hand [5]. This 'BMR' hypothesis has recently been reviewed by Singer [10].

Whatever the equivalences that were used (kidney function = urea excretion = kidney weight = BSA), this theory received great success [3]. Once again, the decreased dispersion of the data was a 'proof' of the performance of the BSA indexing. Nevertheless, this argument may lead to some curiosities. Thus, indexing GFR for BSA leads to GFR values that are comparable between adults and children. In newborns, GFRs indexed for BSA are classically lower and several authors argue that it is linked to the time of maturation for the kidneys [11–16]. This concept of kidney maturation is based on GFR measurements because histological studies on healthy babies have not been done [13]. Nevertheless, the way the GFR is indexed in babies will influence the time of the maturation. This was shown by Rubin in 1949: GFR values in children are similar to adults' values at

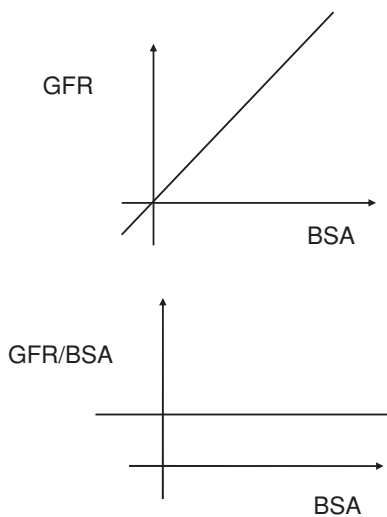


Fig. 1. Illustration of mathematical prerequisites for the use of BSA indexing.

2 years if GFR is indexed for BSA, at 5 months if indexed for kidney weight, before 6 months if body weight is used and after several years if BMR or height is used for indexation. Rubin finally favoured for indexation BSA because ‘it is most commonly used in the literature’, a disappointing argument [16]. The argument of ‘decreasing dispersion of data’ is thus questionable but can also cynically be used against the indexation. Indeed, indexing GFR for BSA or height induces differences in GFR normal values between men and women (logically as men are heavier and higher) that will fully disappear if absolute GFR is used [17]. It is also interesting to underline that differences of GFR normal values are identical in men and women if GFR is indexed for extracellular volume fluid (ECFV) [18]. Although the subject is complex, differences of GFR between genders have been advanced by some authors as an illustration of the fallacy of the BSA indexation [17,18].

The true ‘mathematical’ evidence that could justify the use of indexing for BSA is well known and easy to understand [1,17]. Firstly, the relationship between GFR and BSA must be strong and linear, with a slope not different from 1. The correlation line must pass through the 0 point, without an intercept. Secondly, the relationship between GFR and BSA must totally disappear when GFR is indexed for BSA (Figure 1). Actually, such prerequisites are not found in the literature [17,19–23]. Confirmation of these prerequisites will require the study of a very large sample of ‘nephrologically’ healthy subjects (including lean and obese), which would be difficult. We will thus advance indirect evidence.

Indexing GFR for BSA is misleading: *reductio ad absurdum* from the study of ‘abnormal body size’ patients

Several theoretical arguments do exist against the use of BSA indexing. The inadequacy of such use is, however, difficult to describe in normal body size populations because in them, indexation has nearly no consequences on GFR

Table 1. Bias induced by the MDRD study equation in an obese population with GFR indexed by BSA or not.

	Mean difference between MDRD and indexed GFR	Mean difference between MDRD and absolute GFR
Obesity ($n = 81$, GFR over 60 mL/min)	$+14 \pm 18$ mL/min/ 1.73 m ²	-11 ± 20 mL/min

results [1]. We have thus studied two different abnormal body size populations, i.e. obese and anorectic patients. We will use the topic of estimating GFR by creatinine-based equations (and especially the MDRD study equation) to illustrate our hypothesis [24,25].

First, GFR and creatinine have been measured in 100 obese patients. Of these 100 patients, only patients with measured GFR >60 mL/min were considered for analysis ($n = 81$). Most of these patients were hospitalized for weight reduction. They were frankly obese as their mean weight and body mass index (BMI) were 113 ± 28 kg (range: 76–258 kg) and 41 ± 9 kg/m², respectively. The mean absolute GFR was 101 ± 24 mL/min (measured with the plasma clearance of Cr-EDTA [26]) although the mean indexed GFR was 76 ± 16 mL/min/ 1.73 m² (mean difference between absolute and indexed: 25 ± 14 mL/min). The mean serum creatinine (measured with an IDMS traceable method, the compensated Jaffé method from Roche) was 0.80 ± 0.23 mg/dL. Estimated GFR with the MDRD study equation [$GFR = 175 \times \text{creatinine}^{-1.154} \times \text{age}^{-0.203} \times 0.742$ (if woman)] in this population was 90 ± 22 mL/min/ 1.73 m². If absolute GFR is used as the reference, the MDRD study equation underestimates measured GFR (mean difference: -11 ± 20 mL/min). If the indexed GFR is used as the reference, the MDRD equation overestimates measured GFR (mean difference: $+14 \pm 18$ mL/min/ 1.73 m²) (Table 1). Using indexed GFR as reference, the MDRD study equation will overestimate GFR results in our obese population. Although obese, all the patients included have a measured GFR >60 mL/min. From several studies, it can be concluded that the MDRD study equation systematically underestimates GFR in healthy subjects (and in subjects with ‘normal’ or ‘near normal’ creatinine levels) [24,27,28]. There are no good reasons to believe that this well-established underestimation in low creatinine values does not occur in the obese population. In the same way, there is no reason to believe that the creatinine-based MDRD equation overestimates measured GFR in this population, as it is the case when indexed GFR is considered. GFR underestimation by the MDRD equation is only found in our obese patients when absolute GFR measurements are used. In other words, if indexed GFR is used, we have to conclude that the MDRD study equation overestimates GFR in healthy obese subject, which is astonishing. If absolute GFR is used, our conclusion will be that this equation underestimates GFR in these subjects, which is expected. It could be argued that the MDRD study equation includes BSA indexation and that back-correction is necessary using Dubois’ formula [29]. In the MDRD study, the mean weight was 79.6 ± 16.8 kg [25]. In our former work [1], we have clearly shown that BSA correction has little

influence on GFR results in non-obese patients. However, using this formula, developed and adapted for non obese patients, re-correcting its results by BSA with obese parameters and asserting that the result represents non-corrected GFR are thus a nonsense.

Another example of BSA inadequacy can be done with the other 'extreme population', i.e. anorectic patients [2]. GFR was systematically measured in 27 patients with anorexia nervosa. As expected, the population was young (30 ± 13 years old) and very thin (mean weight: 42 ± 7 kg, mean BMI: 15 ± 2 kg/m²). The mean measured GFR was 68 ± 23 mL/min and the GFR range was large (13–134 mL/min), if absolute GFR was used. In this population, the serum creatinine has a very poor sensitivity to detect GFR < 60 mL/min/1.73 m². Fifty six percent of sensitivity means that one anorectic patient out of two will have kidney disease with serum creatinine in the normal range [2]. This lack of sensitivity is not surprising because serum creatinine concentration is largely dependent on muscular mass, as creatinine is the catabolite of the muscular protein creatine [30]. Because anorectic patients have a decreased muscular mass, their serum creatinine will not rise as expected in renal failure. Now, we are showing our results if indexed GFR for BSA is used in place of absolute GFR. In this condition, mean indexed GFR is logically higher (80 mL/min/1.73 m² versus 68 ± 23 mL/min if absolute GFR). The creatinine sensitivity (determined by ROC curves) to detect GFR < 60 mL/min/1.73 m² would be also higher, i.e. 75%. Based on the well-known creatinine sensitivity in the general population, the sensitivity of creatinine in this anorectic population could be seen as good (or even better) than of the 'normal' body size population [2,31]. This is not possible.

Our last example comes from the recent study of Moranne *et al.* [32]. In their large sample ($n = 1038$), the authors have studied the impact of GFR on chronic kidney disease-related complications. Cr-EDTA was used for measurement of the GFR. Twenty percent of the population was obese (BMI >30 kg/m²). We will focus on one intriguing result. From their multivariate analysis, the authors found that obesity was associated with a lower risk for anaemia. The physiological basis for such a conclusion is questionable. Interestingly, if statistics are done with absolute GFR (and not indexed GFR), the relationship between obesity and risk of anaemia totally disappears (personal communication). From our point of view, indexing GFR will artificially decrease GFR in obese patients. So, obesity will be erroneously considered as a protector against anaemia in kidney disease although these patients have, in fact, no kidney disease at all.

Which alternative to BSA indexation?

Which alternative could be proposed in place of BSA indexing? If indexation must be used (which remains to be proved [6,33]), several ways of indexing have been suggested (reminded in [1]). Among these suggestions, height and ECFV are the most often considered. Regarding height, studies have shown that corrected GFR for height is identical in obese and non-obese populations, whereas corrected

GFR for BSA is inadequately lower in the obese population [34,35]. However, we have already criticized this kind of argument (i.e. lowering dispersion of data). As the range of height in the population is narrower than the range of weight (giants and dwarfs are less numerous than obese or anorectic), it is logical that indexing for height will decrease dispersion of data in the adult population. However, it is not sufficient. Indeed, the fundamental prerequisite (figure 1) has not been studied. Some authors proposed that GFR must be indexed for ECFV [36–39]. Indeed, it seems intuitively better to correct GFR for ECFV because one of the roles of the kidney is to regulate body fluid composition. Nevertheless, ECFVs are not so easy to measure. Indexing GFR for ECFV could only be done when GFR is measured with urinary clearance [18,40]. Moreover, mathematical prerequisites have been poorly studied, too. Peters *et al.* argue that using ECFV indexing had excellent reproducibility on GFR measurement [41], and makes GFR 'normal' values identical in male and women [18,37] and in young infants and adults [38,39]. However, once again, all these 'proofs' are indirect [42]. Even with these limitations and even if indexing for ECFV is still using a ratio and is thus 'mathematically' questionable [6,33], we agree with these authors: indexing GFR for ECFV is of interest and we need additional researches on this topic [1].

Conclusions and perspective

There are several limitations to the use BSA for GFR indexation. This indexation could be considered as a myth. Indeed, it is based on very poor physiological data. Moreover, we have also shown that this indexation may be misleading.

Applying BSA indexation has a 'numerical' effect in the 'abnormal' body size population, i.e. patients with extreme BMI (<18 kg/m² and >30 kg/m²). This effect is probably largely overestimated. Moreover, the estimation of BSA by classical equations is neither precise nor accurate, especially in obese patients [1,4]. So why use it?

For teaching reasons, we have especially insisted on the effect of BSA indexation on the extreme body size population. However, BSA indexation could have consequences even in non-obese studies. For example, Bosma *et al.* have well illustrated that BMI can be considered as a predictor of GFR if GFR is indexed for BSA, but not if GFR is indexed for height [43].

Nowadays, even if other indexations have been proposed [1,18,40], we recommend to use absolute, non-indexed GFR, especially in 'abnormal' body size populations. Definitive arguments for not using BSA indexation will come from studies using appropriate statistics [17] and including a large sample of healthy adults with a large range of body sizes. For example, the large database of living kidney donors recently published by Poggio *et al.* could certainly be used to study indexation (are the figure 1 prerequisites met for BSA, or not?) and the effect of indexation on percentiles of 'normal' reference values [44]. If indexation is not recommended, GFR from children and adults would not be still comparable. The definition of 'normal' GFR values must thus move from simple 'cut-offs'

to percentiles, as it has been shown by Piepsz in children [40] and suggested by others in adults [44,45].

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