The Opposite View

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Indexing of Renal Function Parameters by Body Surface Area: Intelligence or Folly?

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Glomerular filtration rate · Body surface area · Indexation

Abstract
Indexation of glomerular filtration rate (GFR) by body surface area (BSA) is often done without raising any questions. In this article, we will shortly review the limitations of such indexation and illustrate potential errors in clinical practice due to this indexation. Adjusting the GFR by BSA is particularly misleading in patients with abnormal body size (obese and anorectic). We will also insist on the fact that indexation by BSA is not required for the GFR longitudinal follow-up. Additionally, we will discuss the implications and consequences of BSA indexation on the creatinine-based equations, such as the Cockcroft-Gault and the MDRD study equations.

Introduction

Indexing glomerular filtration rate (GFR) for body surface area (BSA) is considered by most nephrologists as a given. However, there are limitations to such an indexation, especially in subjects with extreme body size [1, 2]. In this review, we will describe some of these limitations by providing clinical practice examples where indexing may be misleading. We analyze the feasibility of BSA indexation for measured GFR and its estimation by the Cockcroft-Gault and MDRD study equations.

Indexing Measured GFR

The only logical role of indexing GFR for BSA (or for another variable) is to make comparison possible between subjects with different body size [1]. From a clinical point of view, indexing GFR will significantly impact the GFR results only in patients with 'abnormal' anthropometric data [1]. Therefore, indexing GFR in obese patients would imply both that the relationship between GFR and BSA is linear and with a zero intercept, and that the relation between GFR and BSA disappears after adjusting GFR for BSA [1–4]. This mathematical foundation, however, remains unproven [3]. Moreover, in the obese population, it is essential that the BSA estimation based on weight and/or height is accurate. However, the obese population is the one for which the performances of all these BSA estimation equations are the worst [1–3, 5]. Indexing GFR in cross-sectional studies is thus questionable, but

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this indexation is even more questionable in longitudinal studies when the measured GFR of the same patient is followed up [1, 2, 6]. We will illustrate this assertion with two examples.

First, for an obese patient with a weight of 150 kg, height of 180 cm and BMI of 46.3, a measured (by a reference method) GFR of 150 ml/min would suggest a hyperfiltration state. When indexing for BSA (calculated at 2.8 m^2 with the Haycock equation [7]) is performed, the GFR will be underestimated by 92 ml/min/1.73 m^2 and this would mask the pathologic state of glomerular hyperfiltration [8, 9]. As it has been nicely demonstrated [8], a weight reduction after bariatric surgery could favorably reduce the GFR hyperfiltration (e.g. a reduction of the weight to 90 kg and GFR to 100 ml/min, i.e. a decrease of the GFR hyperfiltration by 33%). If the GFR is indexed with the new BSA of 2.1 m^2, the decrease in GFR hyperfiltration will also be underestimated (only –13% in our example) and the reduction in weight could be erroneously considered as being without significant effect from a 'GFR' point of view [6, 8]. We think that such an indexation does not help to illustrate the effect of obesity on GFR measurements in clinical trials although it is now clear that obesity is a strong risk factor in renal studies using hard endpoints like end-stage renal disease [10].

In contrast, in our second example of a fragile elderly woman with a weight of 45 kg, height of 160 cm, BSA of 1.4 m^2 and BMI of 17.6 requiring cisplatin therapy for ovarian cancer, the therapy must be dose-adjusted according to her GFR. If her measured GFR is 25 ml/min, demonstrating chronic kidney disease (CKD) stage 4, BSA indexing will overestimate the GFR to 31 ml/min/1.73 m^2, thus classifying the patient as stage 3 CKD. Which result should be used for dose adjustment of nephrotoxic therapy and what stage of CKD should be ascribed to the patient? It is more prudent to take into account the result of the patient's actual GFR, not the GFR result that the patient could have if her BSA were 1.73 m^2. Indexation of GFR for BSA can induce relevant differences in patients with abnormal body size. We have to keep in mind that such indexation is not of interest when we need to analyze the individual measured GFR (e.g. for adapting therapy dosage) or to follow the measured GFR of a patient in a longitudinal study. For the longitudinal GFR follow-up of a given subject, absolute GFR without any indexation is actually the best method, especially if the change in weight is mainly due to fat gain or loss.

Indexation of the Cockcroft-Gault Equation

Measuring the GFR may be costly and cumbersome. Thus, estimating GFR by creatinine-based equations is now the most frequent method to evaluate GFR [11, 12]. The Cockcroft-Gault equation has been used since 1976 to estimate GFR [13]. In the original Cockcroft-Gault study, this equation was used to estimate creatinine clearance (not measured GFR), and it was not indexed by BSA. Several authors, especially in recent publications, have corrected the Cockcroft-Gault result for BSA because they wanted to compare it to reference methods indexed for BSA (as it is in the MDRD study equation) [12, 14, 15].

We disagree with this practice for three main reasons. First, Cockcroft and Gault [13] did not index creatinine clearance in their original article. We have no proof that the equation will remain the same (notably regarding the weight variable) if such indexation is used because weight is the most powerful variable in BSA equations [16]. Second, weight is a key variable both in the Cockcroft-Gault and the BSA equations. By indexing for BSA, there is a risk of double correction. In obese patients, the weight variable will induce a strong overestimation of GFR by the Cockcroft-Gault equation and this overestimation will be partially reversed by the BSA indexation. Indeed, the performance of the Cockcroft-Gault equation could be considered to be better when the result is indexed for BSA [15], but this improvement is neither mathematically nor scientifically justified. The third reason may be considered as a 'feeling' more than a strong scientific argument, but it could be of some interest. Actually, one question could be, 'Why has the Cockcroft-Gault equation been so successful?' Is this study unquestionable from a methodological point of view? The answer is doubtless 'no' for a variety of reasons that we will not detail here. We think the Cockcroft-Gault equation was so 'popular' because it was simple to use and calculate. Applying the BSA indexation 'by hand' at the bed of the patient is impossible. So, indexing the Cockcroft-Gault estimate by BSA misrepresents the Cockcroft-Gault equation. Nowadays, if a general practitioner uses the Cockcroft-Gault equation in clinical practice, he will never correct it for BSA.

Indexation in the MDRD Study Equation

An Equation without the Weight Variable

In this section, we will discuss the MDRD study equation, a discussion which could also occur regarding the

recent CKD-EPI equation [12, 17]. Regarding the variables in both the Cockcroft-Gault and the MDRD study equation, there is one striking difference: the weight variable is present in the Cockcroft-Gault equation, but not in the MDRD study equation [12, 13]. The fact that weight does appear in the Cockcroft-Gault equation may be viewed as logical because weight is strongly related to muscular mass and, thus, to serum creatinine. This relationship, however, is less evident in an obese patient because weight also reflects fat mass. Thus, the Cockcroft-Gault equation is not accurate in obese patients when actual weight is used in the formula. This limitation was already underlined by Cockcroft and Gault [13]. Excluding weight from the MDRD study equation has two practical advantages: the MDRD study equation will not (or less) vary according to the BMI (which does not imply that the performance of the MDRD study equation is sufficient in obese patients [18]) and, more importantly in daily practice, the MDRD results can be automatically reported with creatinine results from clinical chemistry.

How can we explain that the weight variable appears in the Cockcroft-Gault, but not in the MDRD study equation? As weight is the major variable in all BSA equations, it is fully logical that this last parameter is not significant in a multivariate regression analysis for predicting GFR when the measured GFR is indexed for BSA, as it is in the MDRD study equation [12]. When we analyze other creatinine-based equations developed to estimate GFR in the past, it is very illustrating that the 'weight variable' only appears in equations developed to estimate GFR not indexed for BSA [13, 19, 20]. On the contrary, weight is not significant as a predictor variable when the reference method is indexed for BSA [12, 21, 22].

Re-Indexing the MDRD Results?

The MDRD formula was developed from an American population that was overweight, but not frankly obese. In the MDRD study, the mean weight and BSA were 79.6 ± 16.8 kg and 1.91 ± 0.23 m^2, respectively. Even if BSA correction has little influence on GFR results in nonobese patients, the MDRD study equation reflects the relationship between serum creatinine and indexed GFR for patients with BSA between 1.5 and 2.4 m^2 [1]. The belief that the relationship between serum creatinine and indexed GFR is the same in patients with higher or lower BSA is purely speculative [16]. Therefore, some authors have proposed to 'de-index' the MDRD results for patients with high BSA, e.g. when adjusting some drug doses [4, 23]. However, using the MDRD equation (which was developed and adapted for nonobese patients), recorrecting its results by the BSA of the obese subject and asserting that the result represents non-corrected GFR does not make sense, especially in patients with a BSA outside of 1.5 and 2.4 m^2 (a fortiori if BSA over 2.4 is due to excess fat body mass).

Example of Japanese Ethnic Factors

Several authors have illustrated the lack of accuracy of the MDRD study equation in Asian populations [24]. For example, an ethnic factor is necessary to correct the trend of the MDRD study equation to overestimate GFR in the Japanese population [25]. As muscular mass in the native Japanese population is expected to be lower than in Caucasians, the observed GFR overestimation may be due to this ethnic difference. However, the findings in Asian populations are not consistent because other authors have found very different results [24]. Actually, in the Japanese study, it is obvious that this ethnic factor corrects the equation results not only for ethnicity, but also for the GFR reference method which was not the same in the Japanese (inulin) and MDRD (iothalamate) studies [24]. Since the MDRD study equation gives a GFR estimation indexed for BSA, this 'BSA integration' is logically applicable for subjects with BSA similar to the MDRD population, i.e. 1.91 ± 0.23 m^2 [12]. In comparison, the Japanese population had a mean BSA of 1.64 ± 0.19 m^2, which is quite different. The ethnic coefficient factor could actually also correct the MDRD results for a different mean BSA in the Japanese population.

Conclusion

Indexing GFR for BSA is often considered as an accepted procedure. In this article, we have elaborated why and how such an indexation could be misleading in particular populations. This is especially the case for obese subjects and when a longitudinal follow-up of their GFR is necessary. In view of the epidemiological finding of a growing prevalence of obesity and the potential long-term consequences of obesity on GFR [10], such considerations should be taken into account and data obtained for GFR indexed by BSA need to be analyzed with caution.

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