Indexing glomerular filtration rate for body surface area in obese patients is misleading: concept and example

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Introduction

Indexing physiological data such as the glomerular filtration rate (GFR) for body surface area (BSA) has two major goals: allowing direct comparison of these data in patients with different body size and also defining values that will be considered as normal [1,2]. The use of BSA for indexing GFR is old and it has become so conventional that one can talk about indexing for BSA as ‘an icon’ in nephrology [3]. Nevertheless, the practice is not immune from criticisms, especially in a population with unusual anthropometric data such as the obese population.

History: more than a century ago . . .

In the late 19th century, physiologists thought that the metabolic rate was proportional to the BSA [4]. Now we know that this assertion is not exact [5–7] but, at that time, it was considered as a law. Measurement of metabolic rate with direct calorimetry is complex. Since 1879, authors have studied different methods to simplify the measurement of BSA which is thought to reflect metabolic rate [8]. The first important study was published in 1915 by the Du Bois brothers [9]. This reference method to measure BSA is ingenious and merits recall. Patients’ bodies were covered with moulds of gummed manila paper. The moulds were cut open, placed flat on photographic paper which was then exposed to sunlight. The unexposed paper was cut and weighed. Knowing the density of the photographic area, the BSA was deduced. The Du Bois brothers first studied five patients and derived a geometric formula estimating BSA with measurements of seven parts of the body (19 measurements in all) (Table 1). Correlation with direct measurement was excellent and this geometric formula is now considered as a reference method by most authors. In the discussion of the original article, it is interesting to note that the authors thought it was unreasonable to expect any formula based on height and weight to be able to overcome the variability of body shape in determining BSA. However, 1 year later, the same authors published, in the same journal, such a formula [10]. To their five initial patients, they added four others. Among the nine patients, there was a 2-year-old child suffering from rickets, one obese patient, one 36-year-old subject with the mental and physical development of a boy of 8, and an 18-year-old with type 1 diabetes and very low body mass index (BMI). Du Bois and Du Bois then developed a formula based on weight and height for BSA estimation with this limited and
BSA is generated by the addition of the seven values obtained (taken with the subject lying on a flat surface).

Mathematically speaking, we can talk, as did Tuner and Reilly, about ‘the fallacy of indexing renal hemodynamics measurements for body surface area’ [7]. Why is indexing for BSA still so used? Why has BSA use been so little criticized? We think that one explanation is the fact that correcting GFR for BSA has very little influence on the absolute values of GFR in the normal weight population. It is thus thought as negligible. For example, the results of GFR measured by isotopic methods ([51Cr]EDTA, single injection method) have been analysed in 40 patients (11 women, mean age 57 ± 18 years) with normal BMI (between 18.5 and 25 kg/m², mean BMI 22.6 ± 1.7 kg/m²) who were hospitalized in our nephrology department (which explains the low mean GFR). The mean difference between absolute GFR and indexed GFR was 1.09 ± 3.66 ml/min (Table 3). This difference was not statistically significant (p = 0.067) and not relevant for physicians. In normal body sized populations, indexing GFR for BSA, although theoretically questionable, has little influence on the final results [1]. However, in longitudinal studies (when the patient is compared with himself), it is important to use the absolute GFR to avoid bias with the indexed GFR due to possible weight change.

Indexing GFR for BSA in obese patients

Many studies have caught nephrologists’ attention about obesity as an independent risk factor of bad

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**Table 1.** Geometrical (or ‘linear’) formula for calculating BSA

| Head | AB × 0.308 |
| Arms | F(G + H + I) × 0.611 |
| Hands | JK × 2.22 |
| Trunk | L(M + N) × 0.703 |
| Thighs | O(P + Q) × 0.508 |
| Legs | RS × 1.4 |
| Feet | T(U + V) × 1.04 |

### Table 2. Most used formulae based on weight and height to estimate BSA (weight in kg, height in cm and BSA in m²)

<table>
<thead>
<tr>
<th>Authors</th>
<th>Formula</th>
<th>No.of patients studied</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Du Bois and Du Bois</td>
<td>0.007184 × weight₀.⁴²⁵ × height₀.⁷₂⁵</td>
<td>9</td>
<td>[10]</td>
</tr>
<tr>
<td>Boyd</td>
<td>0.01788 × weight₀.⁴⁸⁴ × height₀.⁵</td>
<td>197</td>
<td>[13]</td>
</tr>
<tr>
<td>Gehan and George</td>
<td>0.0235 × weight₀.³₁⁴₄₆ × height₀.⁴₂₂₄₆</td>
<td>401</td>
<td>[14]</td>
</tr>
<tr>
<td>Haycock et al.</td>
<td>0.024265 × weight₀.⁵₃⁵ × height₀.₃₉₆₄</td>
<td>81</td>
<td>[15]</td>
</tr>
<tr>
<td>Mosteller</td>
<td>(weight₀.⁵ × height₀.₅⁵)/60</td>
<td>Not determined</td>
<td>[16]</td>
</tr>
<tr>
<td>Livingston and Lee</td>
<td>0.1173 × weight₀.₆₄₆₆</td>
<td>45</td>
<td>[11]</td>
</tr>
</tbody>
</table>

very heterogeneous sample (Table 2). Numerous criticisms were expressed, notably concerning the mathematical and statistical methods used, but one must keep in mind that, at that time, all calculations were made ‘by hand’ [2,5,6,11]. Despite these limitations, this formula seems to be valid and is still the best known and most often used today [12]. Several authors have proposed other formulae studying larger populations [11,13–16] (Table 2), but with no clear practical advantage over the Du Bois formula (except for subjects with weight <10 kg where Haycock or Mosteller formulae are preferred) [2,11,17].

**Indexing GFR for BSA in a ‘normal’ body size population**

Indexing GFR (or any other physiological data) for BSA to avoid variation due to differences in body size necessarily implies that GFR is a linear function of BSA and that the intercept of this linear function is zero. Moreover, when GFR is indexed for BSA, the relationship between indexed GFR and BSA must completely disappear [7,18,19]. These two fundamental prerequisites have been largely ignored by most nephrologists and many physiologists. In fact, the relationship GFR–BSA [7,12,18] and the absence of a relationship between indexed GFR and BSA [7] are not so obvious as previously asserted [20]. Mathematically speaking, we can talk, as did Tuner and Reilly, about ‘the fallacy of indexing renal hemodynamics measurements for body surface area’ [7]. Why is indexing for BSA still so used? Why has BSA use been so little criticized? We think that one explanation is the fact that correcting GFR for BSA has very little influence on the absolute values of GFR in the normal weight population. It is thus thought as negligible. For example, the results of GFR measured by isotopic methods ([51Cr]EDTA, single injection method) have been analysed in 40 patients (11 women, mean age 57 ± 18 years) with normal BMI (between 18.5 and 25 kg/m², mean BMI 22.6 ± 1.7 kg/m²) who were hospitalized in our nephrology department (which explains the low mean GFR). The mean difference between absolute GFR and indexed GFR was 1.09 ± 3.66 ml/min (Table 3). This difference was not statistically significant (p = 0.067) and not relevant for physicians. In normal body sized populations, indexing GFR for BSA, although theoretically questionable, has little influence on the final results [1]. However, in longitudinal studies (when the patient is compared with himself), it is important to use the absolute GFR to avoid bias with the indexed GFR due to possible weight change.

**Indexing GFR for BSA in obese patients**

Many studies have caught nephrologists’ attention about obesity as an independent risk factor of bad
evolution in different nephropathies [21,22]. Some authors even talk about obesity-related nephropathy [23,24]. Thus, GFR measurement is important in this population. Indexing GFR for BSA in such patients has the same theoretical limitations as those described for normal size people. However, the consequences of indexing for BSA are much more important. Indeed, the higher the weight, the higher the BSA will rise and the indexed GFR will decrease [25,26]. For example, the results of GFR measured by [51Cr]EDTA have been reviewed in 81 patients with BMI >30 (56 women, mean age 49 ± 14 years, mean BMI 39.5 ± 7.4 kg/m²). Most of these patients were hospitalized in our metabolic disorders department for a slimming diet regimen (which explains their lower mean age and higher mean GFR than ‘nephrological’ patients). The mean difference between absolute GFR and indexed GFR (according to the Du Bois formula) was 18.2 ± 12.1 ml/min which was highly significant (p <0.0001). The mean difference was even as high as 24.85 ± 14.4 ml/min when analysis was restricted to patients with BMI >40 (n = 33) (Table 3). One can argue that the Du Bois formula is not valid in the clinical setting of obesity. This fact has been discussed [11,14,27]. Livingston and Lee did not have confidence in the Du Bois formula and suggested another formula [11] (Table 2). However, they used as reference for BSA measurement the Du Bois geometrical formula, which seems inadequate in very obese patients [27]. Moreover, when we indexed GFR with this proposed formula, the difference between absolute and indexed GFR was even higher than with the Du Bois formula (Table 3).

Indexing GFR (or other physiological data) in obese patients brings about an unacceptable underestimation of the real GFR. Other authors have illustrated this [25,26,28–30]. Besides explanations already given in non-obese patients, we take arguments from Chagnac et al. ‘Because the number of nephrons does not increase with increasing body fat, increasing obesity must result in an increase in the single-nephron GFR. Absolute GFR reflects this phenomenon whereas correcting GFR for BSA obscures it’ [28]. Indeed, hyperfiltration (found in ±30% of obese patients) is the most evoked (but not the only one) mechanism to explain obesity-related nephropathy [23,28,30,31]. However, when GFR results were analysed in our obese patients with normal creatinine levels and without proteinuria (n = 60), hyperfiltration (GFR >120 ml/min) was noted in 17 patients (28%) if the absolute GFR was used but only in one patient if the corrected GFR was used.

### Other ways to index the GFR?

Due to the limitations of correcting GFR for BSA, other ways of indexing have been proposed. Peters et al. proposed that GFR must be indexed with extracellular volume fluid (ECF) [1,32,33]. Indeed, it seems intuitively better to correct GFR for ECF or total body water (TBW) because one of the roles of the kidney is to regulate body fluid composition [1,18,32]. Nevertheless, ECF or TBW are generally estimated with formulae where weight plays a role, and the validity of such formulae in obese patients has been questioned [3,34,35]. Moreover, Peters et al. studied the paediatric population in particular, and little proof exists for application to adult or obese populations [1,32,33]. In obese patients, lean body mass or ideal body weight (determined by specific formulae) could be considered for indexing the GFR [36,37]. However, a physiological basis is lacking. Each formula has its limitations and bias. Mixing results from two formulae will add bias and is thus questionable. Moreover, it has been shown, with data other than GFR, that using ideal weight can lead to estimation errors [12,38]. As a nephrological example, we can talk about the Cockcroft formula [39] which is known to be unsuitable for creatinine clearance estimation in obese patients [40]. Using ideal body weight in the Cockcroft formula leads to an underestimation of creatinine clearance as high as the overestimation found if using real body weight [40,41].

The most evoked factor to index GFR in obese patients is height. Two studies have shown that corrected GFR (or renal plasma flow) for height is identical in obese and non-obese (‘nephrologically’ normal) populations, whereas corrected GFR for BSA is inadequately lower in obese population [25,26]. However, these interesting results are not sufficient. Indeed, the fundamental prerequisite relationship GFR–height (and the lack of a relationship between GFR indexed for height and height) has not been studied (and it is also the case for lean body mass and ideal body weight). In our limited obese population (n = 81), a linear relationship was not found (weak slope and intercept different from 0).

### Table 3. Mean differences between absolute (ml/min) and indexed (ml/min/1.73 m²) GFR

<table>
<thead>
<tr>
<th>BMI</th>
<th>n</th>
<th>Mean absolute GFR</th>
<th>Mean indexed GFR (Du Bois)</th>
<th>Mean indexed GFR (Livingston)</th>
<th>Mean difference between absolute GFR and indexed GFR (Du Bois)</th>
<th>Mean difference between absolute GFR and indexed GFR (Livingston)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI &lt;20</td>
<td>40</td>
<td>44.47</td>
<td>43.38</td>
<td>43.53</td>
<td>−1.09</td>
<td>−0.95</td>
</tr>
<tr>
<td>BMI &gt;20 but ≤30</td>
<td>81</td>
<td>98.55</td>
<td>81.73</td>
<td>70.94</td>
<td>−18.2*</td>
<td>−27.62*</td>
</tr>
<tr>
<td>BMI &gt;30</td>
<td>33</td>
<td>110.17</td>
<td>87.76</td>
<td>72.29</td>
<td>−24.85*</td>
<td>−37.88*</td>
</tr>
</tbody>
</table>

*p < 0.0001. BMI is given in kg/m².*
for height can thus lead to the same errors as indexing for BSA, especially in the population with high or low height. Moreover, normal values for GFR indexed for height remain to be determined. For all these reasons, we think that correcting GFR for height or ECF in obese (and non-obese) patients is not indicated.

Like other authors, we suggest that the only way to harmonize data and determine normal values is to use regression analysis on a large population sample with different age, sex and body size [7,42,43]. This work needs a multicentric study but, as Turner and Reilly have said, ‘only when this is done will the physician who examines one patient at a time also be able to abandon the practice of indexing’ [7].

Conclusion

We have here commented on and illustrated the concept of indexing physiological data for BSA. Even if, pragmatically, indexing GFR has little influence on GFR values in ‘normal’ body size patients, its use is theoretically questionable [5]. In obese patients, such indexing will lead to important, erratic and unacceptable underestimations of the ‘true GFR’ [25,26,28]. Due to the lack of clear evidence concerning other ways to index (such as using height) and waiting for hypothetical population analysis (regression studies), we really think that absolute, non-corrected GFR must be preferred in daily practice and in clinical studies for the obese (and maybe the overall population).

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Conflict of interest statement. None declared.

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Steroid sparing strategies in renal transplantation

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Keywords: renal transplantation; steroid sparing

Introduction

In the last few years, the aim in the majority of immunosuppressive regimens has been to reduce the incidence and severity of acute rejection, because acute rejection is considered a prognostic factor for poor graft outcome. In the last decade, many renal transplant centres have used triple therapy consisting of a calcineurin-inhibitor (CNI), an antimetabolite, and steroids as induction and maintenance regimens. In this period, nearly all kidney transplant recipients received corticosteroid therapy prior to discharge, although the proportion of patients receiving steroids declined slightly at the end of this period [1]. This trend may reflect concern in the transplant community about the importance of steroid-related morbidity in transplant patients. As a consequence, different attempts have been made to spare steroids in order to reduce co-morbidity. However, steroid sparing strategies may increase the risk of acute and chronic rejection that in turn may jeopardize transplant outcome. In this article we will first review the attempts to spare steroids in renal transplantation in the so-called cyclosporine (CsA) era, and subsequently discuss the strategies tried after the introduction of new xenobiotic immunosuppressants and biological agents.

Steroid-sparing protocols in the CsA era

The main questions raised by steroid-sparing protocols are patient selection, the timing after transplantation and the concomitant immunosuppression.

Initial reports in the CsA era pointed to the increased risk of acute rejection after steroid withdrawal in patients with renal grafts treated with CsA and azathioprine (AZA) [2]. In paediatric patients receiving CsA, stopping steroids was followed by a 56% rate of acute rejection episodes [3]. In a single centre experience with 100 patients, early discontinuation, black race and renal function were identified as risk factors for subsequent rejection episodes after steroid withdrawal [4]. In a multicentre randomized and double-blind, placebo controlled Canadian trial in 523 patients under CsA therapy, prednisone discontinuation at 90 days after transplantation significantly reduced actuarial 5 year graft survival rates.