Predicted creatinine clearance to evaluate glomerular filtration rate in black Caribbean subjects

Ignace Mpio, Maurice Laville, Aoumeur Hadj-Aissa and Jean-Pierre Fauvel

Département de Néphrologie et d’Hypertension artérielle, Hôpital E. Herriot, Lyon, France

Abstract

Background and methods. Although Caribbean people have been a lesser-studied ethnic group than other populations, they have a high burden of hypertension and renal disease. Because Caribbean people have a greater muscle mass than Caucasians, this study examined the accuracy of creatinine-based estimates (creatinine clearance; Ccr and Cockcroft–Gault formula; C-G Cl) of glomerular filtration rate (GFR) in 38 Caribbeans who were matched for age, gender, and GFR, with 38 Caucasian subjects. Patients were considered black Caribbean if at least one of two parents was of black Caribbean origin. GFR values ranging from 5 to 140 ml/min/1.73 m² were measured by inulin clearance. Results were compared using linear correlations and the Bland and Altman methodology to provide better estimates of value dispersion.

Results. Correlation coefficients between C-G Cl and GFR were highly significant in both black Caribbean subjects (r = 0.83, P < 0.001) and Caucasians (r = 0.84, P < 0.001). Similar coefficients were obtained between Ccr and GFR (r = 0.89, P < 0.001 and r = 0.90, P < 0.001, respectively). In spite of these strong correlations, the Bland and Altman representation highlighted huge intra-individual variations in GFR estimation by C-G Cl and by Ccr in both ethnic groups. The underestimation of GFR by C-G Cl was significant in black Caribbeans (−8.6 ± 20 ml/min/1.73 m², P < 0.001) but not in Caucasians (−5.6 ± 20.7 ml/min/1.73 m²). Ccr overestimation of GFR was significant both in Caribbeans (8.7 ± 16.8 ml/min/1.73 m², P < 0.001) and in Caucasians (7.2 ± 15.7 ml/min/1.73 m², P < 0.01).

Conclusions. The C-G formula for estimating GFR yields similar clinical values in black Caribbeans and in Caucasians, but the same limitations were observed in both ethnic groups.

Keywords: black patients; Cockcroft–Gault; creatinine; GFR; renal function

Introduction

The urinary clearance of inulin is widely accepted as the gold standard for estimating glomerular filtration rate (GFR) [1–3]. However, the cost and inconvenience of this technique has led to the more general use of endogenous creatinine clearance (Ccr) or calculated clearance to evaluate GFR [4–6]. Because tubular creatinine secretion increases during the development of renal insufficiency, the overestimation of GFR using Ccr becomes larger as GFR falls. Other parameters such as dietary protein, race, protein catabolism and muscle mass may influence Ccr, resulting in the wide discrepancies that have been reported between Ccr and GFR [1,7]. Of the many formulae that incorporate creatinine concentrations to evaluate GFR, the most convenient and widely used is the Cockcroft–Gault equation (C-G Cl), originally developed in white men [4]. Until now, only two of nine published studies comparing GFR, Ccr and C-G Cl, computing the mean difference between two measurements as recommended by Bland and Altman [8], have been undertaken in African-Americans [5,9]. This type of study has never been performed in the ethnic group of black Caribbeans. In the present study, we used the methodology of Bland and Altman [8] to compare Ccr and C-G Cl to GFR (ranging from 5 to 140 ml/min/1.73 m²) in black Caribbean and Caucasian subjects that were matched for age, gender and GFR.

Subjects and methods

Patients

We included 38 black Caribbean subjects (women and men) who were matched for age (within 3 years), gender and glomerular filtration rate (within 10 ml/min/1.73 m²) with 38 Caucasian patients. Subjects were considered Caucasian if they were the offspring of two Caucasian parents and they were considered black Caribbean if at least one of two parents was of black ethnicity. All patients remained on their
current therapy, which consisted primarily of antihypertensive or anti-inflammatory drugs. None of the patients was using cimetidine or coproducts during the study if they had known serious systemic disease, congestive heart failure, a history of malignant or accelerated hypertension in the past 6 months, pregnancy or lactation, or a history of drug abuse. We obtained informed consent and approval from the Committee for biomedical research for the 56 hypertensive subjects having normal renal function (GFR > 80 ml/min/1.73 m²), while data from the 20 renal disease patients (GFR < 80 ml/min/1.73 m²) were collected retrospectively. Renal impairment was caused mainly by vascular, glomerular and diabetes-related pathologies.

**Methods**

Before the clearance studies, subjects were asked not to change their usual diet. Each protocol began at 8:00 a.m. in a quiet room kept at a constant temperature. After overnight fasting and before the clearance measurements (inulin and creatinine), the subjects were hydrated with 200 ml of tap water to maintain a brisk urine flow. Subjects were placed in a reclining position throughout the study except for active voiding. During the first 30 min, an intravenous cannula was inserted to collect fasting blood samples. Thirty minutes later, inulin (Inutest®, Laevosan, Linz, Austria) was administered as a priming infusion, followed by a sustained infusion to ensure stable plasma concentrations throughout the study, as previously described [10]. After a 45-min equilibration period, three 30-min urine samples were collected by active voiding. Blood samples were collected at each mid-point between active voiding. Inulin clearances were calculated from the mean of three determinations. Also performed were *a posteriori* checks of stable inulin plasma concentrations and inulin clearances. Unstable inulin values were discarded and only reliable inulin clearances were used.

**Measurements**

Office blood pressures were measured using a mercury sphygmomanometer. Inulin was assessed using an adapted, automated colorimetric method that measured the production of fructose from the hydrolysis of inulin by HCl [11]. Inulin clearance provided the GFR. Plasma and urine creatinine were measured according to the Jaffé method, which was automated using a Technicon® auto-analyser (type II). The serum was diluted in sodium chloride (1.8%), was dialysed and then alkalinized (NaOH 0.5 N). Picric acid (1.3%) was then added and optic density was determined (505 nm) in a colorimeter after completion of the reaction.

**Calculations and statistics**

Timed inulin and creatinine clearances were calculated according to standard formulae and corrected for body surface area. The results are presented as the mean of three consecutive determinations. Creatinine clearances were also estimated according to the Cockcroft-Gault formula. All values are presented as means ± SD. Relationships between GFR (inulin clearance) and GFR estimations were assessed by linear regression analysis. For each patient, mean determinations of GFR (mean inulin and measured or calculated creatinine clearance) were plotted against differences (inulin minus measured or calculated creatinine clearance) according to the Bland and Altman methodology. Student’s *t*-tests were used to compare values between groups. A *P*-value < 0.05 was considered significant.

**Results**

As shown in Table 1, the main clinical characteristics of the 38 Caribbeans and 38 Caucasians were similar. Mean body mass index (BMI) was above normal in both groups. The range of GFR was very large, from 5 to 140 ml/min/1.73 m². In each group, 10 subjects had GFR lower than 80 ml/min/1.73 m². Mean creatininemia and GFR did not differ between the groups. In Caribbeans, GFR was significantly correlated with C-G Cl (r = 0.83, *P* < 0.001) and with C_cr (r = 0.89, *P* < 0.001). Similarly, in Caucasians, GFR was significantly correlated with C-G Cl (r = 0.84, *P* < 0.001) and with C_cr (r = 0.90, *P* < 0.001). As shown in Figure 1, C-G Cl underestimated GFR by $-8.6 \pm 20.0$ ml/min/1.73 m² in Caribbeans and by $-5.6 \pm 20.7$ ml/min/1.73 m² in Caucasians. Underestimation of GFR by G-G Cl was significantly different from zero only in Caribbeans (*P* < 0.01). As shown in Figure 2, C_cr overestimated GFR by $8.7 \pm 16.8$ ml/min/1.73 m² in Caribbeans and by $7.2 \pm 15.7$ ml/min/1.73 m² in Caucasians. Overestimation of GFR by C_cr was significantly different from zero in both Caribbeans and Caucasians (both *P* < 0.001). Filtered (9.65 ± 3.04 vs $9.04 \pm 2.50$ mmol/min) and secreted (1.19 ± 1.91 vs $1.22 \pm 2.15$ mmol/min) creatinine were not significantly different between Caribbeans and Caucasians. Figure 3 shows that GFR in both groups was significantly and negatively correlated (r = 0.527, *P* < 0.001 and r = 0.734, *P* < 0.001 in Caribbeans and Caucasians, respectively) with tubular creatinine flux (creatinine was secreted when renal function was altered but slightly reabsorbed if GFR was normal). Estimations of GFR by C-G Cl and by C_cr were

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Black Caribbeans</th>
<th>Caucasians</th>
<th><em>P</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>38</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>Gender (men/women)</td>
<td>13/25</td>
<td>13/25</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>45 ± 8</td>
<td>46 ± 7</td>
<td>NS</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>29 ± 5</td>
<td>28 ± 6</td>
<td>NS</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>144 ± 28</td>
<td>137 ± 24</td>
<td>NS</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>84 ± 13</td>
<td>82 ± 13</td>
<td>NS</td>
</tr>
<tr>
<td>Creatininemia (µmol/l)</td>
<td>125 ± 84</td>
<td>123 ± 89</td>
<td>NS</td>
</tr>
<tr>
<td>Creatinine excretion (µmol/24 h)</td>
<td>15.6 ± 5.0</td>
<td>13.4 ± 5.1</td>
<td>NS</td>
</tr>
<tr>
<td>GFR (ml/min/1.73 m²)</td>
<td>91 ± 36</td>
<td>91 ± 36</td>
<td>NS</td>
</tr>
<tr>
<td>C_cr (ml/min/1.73 m²)</td>
<td>100 ± 36</td>
<td>98 ± 33</td>
<td>NS</td>
</tr>
<tr>
<td>C-G Cl (ml/min/1.73 m²)</td>
<td>82 ± 33</td>
<td>86 ± 38</td>
<td>NS</td>
</tr>
</tbody>
</table>

SBP, systolic blood pressure; DBP, diastolic blood pressure; NS, non-significant.
significantly different in each group ($P<0.001$), but there were no differences in $C_{cr}$ and in C-G Cl between ethnic groups.

**Discussion**

Higher muscle masses in black subjects may lead to erroneous estimates of GFR when using the C-G Cl formula. Of the few studies reporting GFR estimation methods in African-Americans [1,5,7,9], this is the first conducted in black Caribbeans. In our study, C-G Cl and $C_{cr}$ provided similar estimations of GFR in black Caribbeans and in Caucasians. Correlations between GFR and both $C_{cr}$ and C-G Cl were highly significant ($P<0.001$) in both Caribbeans and Caucasians. However, the Bland and Altman methodology revealed huge intra-individual variations in GFR estimations in both ethnic groups when using either the C-G or the $C_{cr}$ formula.

The mean underestimations of GFR were slightly higher in black Caribbeans than in Caucasians with
similar SD. This finding is consistent with a previous report in African-Americans [5], and underestimation of GFR in blacks has been ascribed to higher creatinine excretions [9]. Although we found greater muscle mass, estimated by 24-h creatinine excretion in black Caribbeans, this did not attain significance ($P = 0.08$). Whereas filtered creatinine was slightly but non-significantly higher in black Caribbeans than in Caucasians, tubular secretion of creatinine was similar in both groups (Figure 3).

Simultaneous measurement of urinary creatinine clearance allowed an accurate comparison with GFR that was free of collection errors because the protocols shared the same urine collection times and volumes. Timed creatinine clearances produced similar overestimations of GFR and similar SD in both groups. In previous studies with African-Americans, C-G Cl estimations produced a wider scatter than did $C_{cr}$ when these were measured simultaneously with GFR [5]. Overestimations of GFR by $C_{cr}$ are usually attributed to a tubular secretion of creatinine, occurring especially in chronic renal impairment [1–4]. The Bland and Altman methodology, showing a huge dispersion of GFR estimations, indicates that confidence in calculated clearances is very low for individual subjects and that this low confidence is independent of ethnic groups.

In conclusion, the C-G formula for estimating GFR yields the same clinical values in black Caribbeans and in Caucasians but the same limitations were seen in both ethnic groups.

Conflict of interest statement. None declared.

References


Received for publication: 19.7.02
Accepted in revised form: 2.12.02